

Exploitation in Clinical Drug Trials

by

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ABSTRACT

With the number of internationally-run clinical drug trials increasing, the double standards between those in developed nations and those in developing nations are being scrutinized under the ethical microscope. Many argue that several pharmaceutical companies and researchers are exploiting developing nation participants. Two issues of concern are the use of a placebo control when an effective alternative treatment exists and the lack of drug availability to the country that hosted the clinical trial should the experimental drug prove effective. Though intuitively this seems like an instance of exploitation, philosophically, exploitation theories cannot adequately account for the wrongdoing in these cases. My project has two parts. First, after explaining why the theories of Alan Wertheimer, John Lawrence Hill, and Ruth Sample fail to explain the exploitation in clinical drug research, I provide an alternative account of exploitation that can explain why the double standard in clinical research is harmful. Rather than craft a single theory encompassing all instances of exploitation, I offer an account of a type, or subset, of exploitation that I refer to as comparative exploitation. The double standards in clinical research fall under the category of comparative exploitation. Furthermore, while many critics maintain that cases of comparative exploitation, including clinical research, are mutually beneficial, they are actually harmful to its victims. I explain the harm of comparative exploitation using Ben Bradley's counterfactual account of harm and Larry May's theory of sharing responsibility. The second part of my project focuses on the "standard of care" argument, which most defenders use to justify the double standard in clinical research. I elaborate on Ruth Macklin's position that advocates of the "standard of care" position make three faulty assumptions: placebo-controlled trials are the gold

standard, the only relevant question responsive to the host country's health needs is "Is the experimental product being studied better than the 'nothing' now available to the population?", and the only way of obtaining affordable products is to test cheap alternatives to replace the expensive ones. In the end, I advocate moving towards a universalizing of standards in order to avoid exploitation.

DEDICATION

For my parents, Ramon and Lori Fundora, and my sister, Nichole Fundora, whose continued support and love gave me the strength to come this far.

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Chapter 1: THE PROBLEM

Introduction

In the past two decades, clinical drug research run abroad has dramatically increased. From 1990 to 1999, the number of countries hosting research involving human subjects jumped from twenty-nine to seventy-nine, the largest growth occurring in Russia, Eastern Europe and Latin America.¹ By 2004, the Food and Drug Administration (FDA) estimated that those drug companies petitioning for FDA approval for new products were launching over sixteen hundred new trials overseas every year.² Of the 141, 132 trials registered on ClinicalTrials.gov from 2000 to February 2013, only forty-one percent of the studies were run only in the United States. Six percent were run both inside and outside of the United States, and forty-three percent were only run outside of the United States.³

Several factors have generated the migration abroad, particularly to “low-cost” countries. Throughout this dissertation, those countries shall be referred to as developing countries. The primary motivator for moving drug trials abroad has been to cut costs. Thomas Fogarty, inventor and founder of Mountain View’s Fogarty Institute for Innovation, stated that many companies are looking at regions where labor costs are drastically lower, such as Paraguay, Argentina, and Mexico. He states, “[y]ou can find people there who are well-trained in their work and do follow-up with patients. It’s an

¹ Ruth Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge: Cambridge University Press, 2004), 7.

² Sonia Shah, *The Body Hunters: Testing New Drugs on the World’s Poorest Patients* (New York: The New Press, 2006), 7.

³ “Trends, Charts, and Maps,” ClinicalTrials.gov, last reviewed August 2012, <http://www.clinicaltrials.gov/ct2/resources/trends>.

affordable process in those places.”⁴ With the process of bringing a new drug to market costing up to \$1 million, venture-backed companies want to save as much money as possible in order to maximize profits gained from the new drug.⁵ GlaxoSmithKline’s CEO in 2004 claimed \$200 million a year in savings due to the relocation of around thirty percent of its trial business to “low-cost” countries such as Poland and India.

While cheaper labor and resources accounts for part of that cost, the increased speed at which they are able to run trials accounts for the other. Trial participants are often hard to find. In 2006, trouble finding participants led to an average 4.6 months lost per trial.⁶ In 2002, it was reported that less than four percent of cancer patients, who generally have the most to gain from experimental treatments, volunteer for trials.⁷ While recruitment is slow in the United States, recruitment abroad is much more rapid. When little healthcare exists in a country, people leap at an opportunity to receive treatment. For example, Quintiles was able to find 3,000 volunteers in South Africa for an experimental vaccine study in just nine days.⁸ For many clinical trials are the only the participants only way to have modern medical care as either their country lacks the resources for modern medical care or the participants cannot afford it as they have no insurance. As Laxminarayn Bhat, founder and CEO of San Jose-based Reviva

⁴ David Goll, “Clinical trials move overseas to speed process, save money,” *Silicon Valley Business Journal*, April 13, 2012, accessed April 17, 2013, <http://www.bizjournals.com/sanjose/print-edition/2012/04/13/clinical-trials-move-overseas-to-speed.html?page=all>.

⁵ Goll, ““Clinical trials move overseas to speed process, save money.”

⁶ Beasely, “Recruiting,” 2006, quoted in “Clinical Trial Facts & Figures,” The Center for Information & Study on Clinical Research Participation, accessed April 17, 2013, http://www.ciscrp.org/professional/facts_pat.html.

⁷ Shah. *The Body Hunters*, 4.

⁸ Shah. *The Body Hunters*, 9.

Pharmaceuticals Inc., explains, “[h]ere in the U.S., most people have insurance, so it’s difficult to get volunteers. . . . If you can get one or two patients, you’re doing well. If you go to Russia or some places in Asia, where people are paying for health care out of pocket, it’s much easier to find people to participate in trials.”⁹

Moreover those participants in developing nations are less likely to complain and drop out of a trial. In 2003, Vijai Kumar, head of a New Delhi-based industry trial center, boasted that they have retained 99.5 percent of subjects enrolled.¹⁰ John Wurzlemann, MD recounts a study completed in both the United States and Russia in which venograms were used. Venograms require patients to have a surgically inserted intravenous catheter to administer contrast-heightening chemicals so that x-rays could be more easily read. The invasive venogram had been largely replaced by noninvasive CT scans and MRIs in the United States. The portion of the study in Russia not only received more patients, but patients were very willing to have the venogram procedure as no other alternative existed.¹¹

An additional financial advantage is that researchers are able to run placebo control trials in developing nations that they would not otherwise be able to in developed nations. In those cases, a placebo control could not be used because an alternative proven treatment exists on the market in developed worlds. To run a placebo control when an alternative exists and is available in that country is considered unethical, particularly by the FDA. However, if the drug is not available on the market, such as in many developing nations, then it has been permissible to use a placebo control. By

⁹ Goll, ““Clinical trials move overseas to speed process, save money.”

¹⁰ Shah. *The Body Hunters*, 9.

¹¹ Shah. *The Body Hunters*, 9.

permissible, I mean that the trials that use a placebo control in those instances - where the alternative treatment is not available in that nation - have passed FDA inspection. As will be discussed at length in Chapter 3, the FDA passes placebo control trials faster than active control trials. That is because trials with a placebo control have efficacy data that is more readily acceptable for the FDA. As we shall see, there is much debate as to whether an active control trial can produce the efficacy data that placebo controls do. There are high costs associated with delay of a drug's release on a market. In 2008, it was estimated that a pharmaceutical company loses \$8 million each day that a drug release on the market is delayed.¹² As a result, companies want to pass through the FDA approval process as fast as possible, which means providing them with the type of data they are most ready to accept, which has historically been placebo control data.

There are also scientific advantages of running trials in developing nations. Subjects in developing nations have significantly less access to healthcare than in other more industrialized nations. As a result, they are exposed to fewer drugs than subjects in industrialized nations. This yields more reliable results for the experimental drug, as there is little worry about the experimental drug interacting with others. As one industry spokesperson is quoted as saying, “[y]ou want patients with no other disease states and no other treatments. Then you can say relatively clearly that whatever happens to those patients is from the drug.”¹³

¹² Beasley, "Recruiting," 2008, quoted in "Clinical Trial Facts & Figures," The Center for Information & Study on Clinical Research Participation, accessed April 17, 2013, http://www.ciscrp.org/professional/facts_pat.html.

¹³ Sonia Shah, "Globalizing Clinical Research," *The Nation* (July 1, 2002): 23, quoted in Ruth Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge: Cambridge University Press, 2004), 7.

With the increase in drug trials, one might assume that the developing world is getting healthier; however, that is not the case. Americans have been getting healthier. Between 1965 and 1996 death rates from blocked arteries dropped by seventy-four percent, from heart disease by sixty-two percent, and from hypertension by twenty-one percent.¹⁴ The Center for Disease Control reports that the death rate in the United States has dropped by sixty percent between 1935 and 2010.¹⁵ They also reported that in 2010 the top five leading causes of death were heart disease, cancer, chronic lower respiratory disease, stroke, and accidents. The developing world, on the other hand, is not getting healthier. The top five causes of death for low-income countries are, in order, lower respiratory infections, diarrheal diseases, HIV/AIDS, ischaemic heart disease, and malaria.¹⁶ Many of the diseases leading to death in the developing world have been minimized in the developed world. For example in 2000, more than one million people, mostly children, died of Malaria in Africa, whereas only 1200 were diagnosed with Malaria in the United states, most occurring in immigrants or travelers.¹⁷ Because the market for infectious and tropical diseases is small, little money is spent on researching those diseases. As Alan Wertheimer notes, ninety percent of the global research budget is spent on illnesses that cause ten percent of the world's disease burden; whereas, ten

¹⁴ Shah. *The Body Hunters*, 44.

¹⁵ Donna L. Hoyert, "75 years of mortality in the United States," *1935-2010 NCHS Data Brief*, 88 (Hyattsville, MD: National Center for Health Statistics, 2012), accessed April 17, 2013, <http://www.cdc.gov/nchs/data/databriefs/db88.htm>.

¹⁶ "The top 10 causes of death," World Health Organization, updated June 2011, <http://www.who.int/mediacentre/factsheets/fs310/en/index.html>.

¹⁷ Macklin, *Double Standards in Medical Research in Developing Countries*, 9.

percent of the global research budget is spent on illnesses affecting ninety percent of the world's population.¹⁸

The increasing exportation of clinical research to developing nations, which best serves the needs of the developed world, demands higher scrutiny under the ethical microscope. Many argue that researchers and pharmaceutical companies are exploiting developing nations. Particularly, one questions the conduct of researchers and pharmaceutical companies when different standards are used in a developing nation versus a developed nation. On the face of it having two standards for conducting clinical research trials, one with much more lax standards, seems like widespread exploitation, exploitation theories cannot adequately account for the wrongdoing in these cases. That is because it seems as if the victims in the case of clinical trials are benefitting rather than being harmed as they have the opportunity to receive healthcare that they would otherwise not receive. The literature refers to cases of exploitation where the victim benefits as mutually beneficial exploitation. Mutually beneficial exploitation is a source of difficulty for many exploitation theories because it is difficult to understand why it is morally wrong.

In this dissertation, I argue that while existing theories may not be able to explain the exploitative nature of the double standards in clinical research, researchers and pharmaceutical companies are exploiting developing nations. Specifically, I argue that clinical research is a type of exploitation I call "comparative exploitation." While instances of comparative exploitation, like clinical research, may seem mutually

¹⁸ Alan Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens* (Oxford Scholarship Online, 2010), 7, accessed April 17, 2013, <http://lib.myilibrary.com.ezproxy1.lib.asu.edu?ID=294138>.

beneficial, they are actually harmful to its victims. Moreover, I will also contend that the traditional response to charges of exploitation, the “standard of care” response, fails to justify the double standards. While considering the exploitative nature of clinical research in developing nations, I will look at two particular issues - placebo-controlled trials and the availability of the experimental drug should it be proven effective.

In the rest of this chapter, I will offer background information on clinical research and set up the problem of exploitation in developing nations. After offering information on the developed versus developing country distinction and the history of guidelines regulating clinical research, I will explain the double standard between trials in developed nations and developing nations. Specifically, once I explain two case studies, I will explore the issues of placebo controls, drug availability, and consent. I will, then, explain why exploitation is the appropriate model for this situation. Finally, I will briefly explain the topics of the remaining chapters.

Developed versus Developing

The terms “developed” and “developing” are terms typically used to compare nations’ economic levels, with developed countries at the higher wealthier levels and developing at the lower poorer levels. Developed nations are also often called “industrialized,” as opposed to “industrializing” to indicate the process of becoming an industrialized economy, or “non-industrialized.” Of the 158 nations that are members of

the World Trade Organization, about two-thirds are self-proclaimed as developing,¹⁹ and 34 nations of that two-thirds are recognized as least-developed countries.²⁰

Despite their widespread use, there is not hard and fast line distinguishing between developed, developing and least developed nations. Rather than a categorization, it seems that the distinctions ought to be more of a sliding scale with developed and least developed at opposite ends so as to reflect the distinctions between nations. There is a trend, however, when discussing specific countries to label Western Europe, North America, Japan Australia, and New Zealand as developed and label all others as developing. There is a lot of controversy concerning these labels. For example, is China a developed or a developing nation? If it is a developing nation, than ought it to be categorized under the same label as more economically impoverished nations, such as Ethiopia? Ruth Macklin argues that, particularly for evaluating the research enterprise, the categorization depends on which features of the country we wish to talk about. She explains,

[i]t is appropriate to lump together countries that are resource-poor, since neither the government nor the majority of citizens can afford medical treatments that become largely available to residents of wealthier countries once research is concluded. It is appropriate to lump together countries that have few trained scientists and little experience of conducting biomedical research. And it is appropriate to lump together countries that lack ethical guidelines for research and have little or no capacity for conducting ethical review of research conducted there by industry or by scientists from industrialized countries.²¹

¹⁹ “Understanding the WTO: Developing Countries,” World Trade Organization, accessed April 17, 2013, http://www.wto.org/english/thewto_e/whatis_e/tif_e/dev1_e.htm.

²⁰ “Understanding the WTO: The Organization,” World Trade Organization, accessed April 17, 2013, http://www.wto.org/english/thewto_e/whatis_e/tif_e/org7_e.htm.

²¹ Macklin, *Double Standards in Medical Research in Developing Countries*, 10.

Macklin has picked out the relevant characteristics of comparison that clinical research ethics literature discusses. Thus, those are the factors I will rely on when comparing developing and developed nations throughout this dissertation. At its core, the chief distinction between the two is, as Macklin describes, in developed nations the majority of the population has the opportunity to access successful products of research and the majority of the population in developing nations do not have that opportunity.²²

Guidelines

Throughout the dissertation I will make reference to specific guidelines that regulate international research conducted on human subjects. In chapter 4 on the “standard of care” debate, I analyze three specific sets of guidelines: the Declaration of Helsinki, the Council for International Organizations of Medical Sciences, and the FDA. Here I will give a brief background to the development of the guidelines and their purposes.

Declaration of Helsinki

In June 1964, the World Medical Association at a meeting in Helsinki adopted a code of ethics on human experimentation, known as the Declaration of Helsinki. The original Declaration of Helsinki has roots in the Nuremberg Code - a code of ethics on human experimentation emerging from the exposure of horrific experiments on

²² Macklin, *Double Standards in Medical Research in Developing Countries*, 11

concentration camp prisoners at the 1947 Nuremberg trials.²³ In 1975 the first revision of the Declaration was made and was signed by the United States and thirty-four other countries. As Sonia Shah describes, the revised Declaration urged

voluntary informed consent, the use of independent ethics committees, and that investigators prioritize, their subjects' well-being above all other concerns, including 'the interests of science and society.' In the interests of justice, the declaration suggested, research subjects should be assured of access to the best health interventions identified in the study, and that their societies enjoy a 'reasonable likelihood' of benefiting from the results of the experiment.²⁴

Minor revisions were made to the Declaration in 1983, 1989, and 1996. In 2000, the World Medical Association made another major revision to the Declaration. While retaining the primacy of the individual, the 2000 revision increased awareness of public health needs. Specifically, the revision removed the distinction between "therapeutic" and "non-therapeutic" research. That distinction was premised on most medical research being "therapeutic," meaning it is intended to benefit the research subject. The 2000 revision, on the other hand, contends that the purpose of research is the advancement of knowledge for the benefit of future patients. That purpose and its limitations for the health needs of subjects are demonstrated through double-blinded clinical trials. The 2000 revision also added an entirely new concept; researchers and sponsors had a responsibility to provide benefits to populations. Though the nature of those benefits is

²³ Robert V. Carlson, Kenneth M. Boyd, and David J. Webb, "The revision of the Declaration of Helsinki: past, present, and future," *British Journal of Clinical Pharmacology*, 57, no. 6, (June 2004): 696.

²⁴ Shah. *The Body Hunters*, 75-76.

not specified, as John R Williams argues, the addition adds a public-health component to research ethics.²⁵

In 2008, the Declaration was revised again in order to incorporate new requirements relating to the registration of clinical trials and the reporting of their results. The purpose of those requirements is to reduce publication and reporting bias, which will provide reliable evidence for decision-making. This addition represents the medical community's firm commitment to transparency to help rebuild trust in medical research, which had been damaged by controversies.²⁶ Those include the use of placebo-controlled trials, the standard of care argument, and post-trial obligations in research in developing countries.

The Council for International Organizations of Medical Sciences (CIOMS)

In 1949, the World Health Organization (WHO) and the United Nations Educational Scientific and Cultural Organization (UNESCO) formed CIOMS, an international, non-governmental, non-profit organization. With its over 55 international, national and associate member organizations as of 2010, it represents many of the biomedical disciplines, national academies of sciences and medical research councils.

CIOMS' main objectives are:

- To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;

²⁵ John R Williams, "The Declaration of Helsinki and public health," *Bull World Health Organ* 86, no. 8 (August 2008): 650-651.

²⁶ Karmela Krieza-Jefric and Trudo Lemmens, "7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials," *Croatian Medical Journal* 50, no. 2 (April 2009): 105.

- To maintain collaborative relations with the United Nations and its specialized agencies, in particular WHO and UNESCO
- To serve the scientific interests of the international biomedical community in general
- To achieve its objectives, CIOMS has initiated and coordinates the following main long term programs: [Bioethics; Health Policy, Ethics and Human Values - An International Dialogue, Drug Development and Use; International Nomenclature of Diseases].²⁷

In the late 1970s, CIOMS, in association with WHO, began its work on ethics related to biomedical research. Its goal was to establish guidelines that would explain how the ethical principles concerning biomedical researching involving human subjects, as laid out in the Declaration of Helsinki, should be applied, especially in developing nations. This led to CIOMS publishing the *Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects* in 1982. Those guidelines were revised in the early 1990s, leading to two sets of guidelines: in 1991, *International Guidelines for Ethical Review of Epidemiological Studies*; and, in 1993, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

Those guidelines covered mainly when a comparator could be used other than the established effective therapy and clinical trials with external sponsors and investigators that were conducted in developing nations. However, there were ethical situations for which CIOMS had no guidelines, particularly the perceived need for low-cost, technologically appropriate, public-health solutions in developing nations. That was especially true for HIV/AIDS treatments or vaccines that developing nations could not

²⁷ “About Us,” Council for International Organizations of Medical Sciences, accessed April 17, 2013, <http://www.cioms.ch/index.php/2012-06-07-19-16-08/about-us>.

afford. As a result, in 2002 the CIOMS updated its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* to reflect those issues.²⁸

United States' Guidelines

Prior to 1972, there was little formal federal legislature or guidelines reviewing researchers' experimentation protocols or obtaining subject consent. Congress passed legislation in 1962 requiring subject consent for any study seeking FDA approval for new drugs; however, the legislation was largely ineffective because it allowed for exceptions when obtaining consent was "not feasible" or was not in the best interest of the subject.²⁹ Subsequently, in 1966, a directive was issued by the Surgeon general stating that "clinical researcher would be supported only if the judgment of the investigator would be subject to prior review by the institutional associates concerning the issues of: (1) the rights and welfare of research subjects; (2) the appropriateness of the methods used to assure informed consent; and (3) the risk and medical benefits of the investigation."³⁰ There were later revisions of that policy that required assurances that investigations complied with community laws and gave "due consideration to pertinent ethical issues."³¹ While the review committees were typically comprised of scientists and physicians by 1969, the

²⁸ "International Ethical Guidelines for Biomedical Research Involving Human Subjects," Council for International Organizations of Medical Sciences, accessed April 17, 2013, http://www.cioms.ch/images/stories/CIOMS/guidelines/guidelines_nov_2002_blurb.htm.

²⁹ Jesse A. Goldner, "An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously," in *The Ethics and Regulation of Research with Human Subjects*, ed. Carl H. Coleman, Jerry A Menikoff, Jesse A. Goldner, and Nancy Neveloff Dubler (Newark: LexisNexis, 2005), 51-52.

³⁰ Goldner, "An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously," 52.

³¹ Goldner, "An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously," 52.

guidelines required that committee membership reflect diverse backgrounds and that members be competent in the ways of “institutional regulations, relevant law, standards of professional practice, and community acceptance.” The Department of Health, Education and Welfare, in May 1974 passed regulations requiring that no committee could be comprised in its entirety of members from a single professional group or institution employees.³²

That same year, the U.S. Senate passed the National Research Act of 1974 that established the Institutional Review Board and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In order to protect the rights of human subjects, the Institutional Review Board was set to review both biomedical and behavioral human subject research that is conducted or sponsored by the Federal Government. While the requirement only applies to federally-funded research, other institutions such as universities, medical schools, and research hospitals have “negotiated” these assurances with the federal government, promising to conform with the regulations and applying them to all research no matter the source of funding.

The National Commission’s task was to identify basic ethical principles that would underlie the conduct of research involving human subjects and provide guidelines that could apply to such research. From this charge, the National Commission issued the 1979 *Belmont Report* (the Report). The Report identified three philosophical principles, which are relevant to human subject research: respect for persons, beneficence, and

³² Goldner, “An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously,” 52.

justice.³³ As the Report argues, respect for persons, minimally, encompasses two ethical convictions “first, that individuals should be treated as autonomous agents, and second that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.”³⁴

While “beneficence”, as the Report points out, is usually understood as acts of kindness or charity that go beyond strict obligation, the Report intends beneficence to be understood as a stronger obligation. Expressions of beneficence, the Report argues, can be understood as the following two rules: “(1) do not harm and (2) maximize possible benefits and minimize possible harms.”³⁵

The Report understands justice in in multiple senses, including “fairness in distribution,” “what is deserved,” and “equals ought to be treated equally.” It argues that an injustice occurs when “some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.”³⁶ While, it does not argue for one specific theory of justice, it does maintain that in light of events such as the Tuskegee

³³ Goldner, “An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously,” 52-53.

³⁴ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research,” April 18, 1979, accessed April 17, 2013, <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.

³⁵ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research,”

³⁶ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research,”

syphilis study and Nazi experiments on concentration camp prisoners that justice is relevant to research involving human subjects.

FDA

The FDA's primary responsibility, as assigned by Congress, is to determine when certain types of treatments - such as drugs, devices, and biologics - can be marketed in the United States. As part of that responsibility, the FDA must decide on what threshold of evidence is required, along with the types of studies that can produce that evidence, to prove that a new treatment is safe and effective for treating a particular medical problem. Once a study has been approved by the FDA to be conducted, the results must be presented to an expert panel that makes recommendations to the FDA on whether the treatment is safe and effective.³⁷

Prior to 2000, the FDA largely incorporated the principles of the Declaration of Helsinki into its guidelines. However, the FDA was unhappy with the revisions of the Declaration between 2000 and 2004. During that time, the FDA referred to the 1989 version of the Declaration, which the World Medical Association considered invalid. The FDA was reacting, in particular, to the addition of two paragraphs (29 and 30), which if adopted by the FDA, there would be a limit on the use of placebos in drug trials and an increase in responsibilities of trials sponsors toward research participants.³⁸³⁹ In 2008,

³⁷ Carl H. Coleman, Jerry A Menikoff, Jesse A. Goldner, and Nancy Neveloff Dubler, ed., *The Ethics and Regulation of Research with Human Subjects* (Newark: LexisNexis, 2005), 142.

³⁸ Howard Wolinsky, "The battle of Helsinki: Two troublesome paragraphs in the Declaration of Helsinki are causing a furor over medical research ethics," *Science and Society* 7, no. 7 (2006): 670

the FDA took a further step and “removed all reference to the Declaration in its approval requirements for drugs and biological products studied outside of the United States.”⁴⁰ Instead, the FDA adopted the International Conference on Harmonisation Good Clinical Practice as its new regulatory standard, justifying its decision by arguing that it was harmonizing its regulations with a global standard.⁴¹

The Problem

In order to understand the ethical concerns of clinical drug trials. Let us look at two specific trials that are popular in clinical research literature: AZT and surfaxin.

AZT

The debate over international clinical trial standards sparked in the early 90’s. In 1994 the New England Journal of Medicine published the results of the AIDS Clinical Trials Group Study 076. The study demonstrated that the drug zidovudine (AZT) reduced the rate of transmission of HIV from pregnant women to their newborn infants by two thirds.⁴² By 1997, AZT was associated with a fifty percent decrease in HIV transmission in the United States; however, the potential of AZT was unrealized in

³⁹ There will be extensive discussion of those paragraphs in chapter 4

⁴⁰ Annette Rid and Harald Schmidt, "The 2008 Declaration of Helsinki—First among Equals in Research Ethics?," *The Journal of Law, Medicine & Ethics* 38, no. 1 (2010): 143.

⁴¹ Michael Goodyear, Trudo Lemmens, Dominique Sprumont, and Godfrey B. Tangwa, "The FDA and the Declaration of Helsinki: A New Rule Seems to Be More About Imperialism than Harmonisation," *British Medical Journal* 338 (2009): 1157.

⁴² Zidovudine’s brand name is Retrovir and was formerly called azidothymidine [AZT]. Zidovudine may also be abbreviated as (ZDV) Most of the literature refers to this drug as AZT, which is what I will refer it throughout the remainder of this dissertation. For more information, see <http://www.rxlist.com/retrovir-drug.htm>.

developing nations, especially in Asia and sub-Saharan Africa, primarily because of AZT's high cost.⁴³ AZT was originally released on the market as Retrovir in 1987 as a treatment for AIDS by a company that would later become a part of GlaxoSmithKline. Even though a sizable public investment had gone into the development of AZT, the company charged AIDS patients \$8,000 for a year's worth of treatment.⁴⁴

In an effort to find a less expensive treatment, clinical trials were run to test less expensive interventions to prevent perinatal transmission of HIV- such as lowering the dose of AZT given, decreasing the number of doses a patient took of AZT, and testing alternative interventions. In September 1997, Peter Lurie, Sidney Wolfe, and Marcia Angell published articles in the *New England Journal of Medicine* criticizing on ethical grounds the design of those trials. Lurie and Wolfe identified eighteen randomized, controlled trials to prevent perinatal transmission of HIV - two in the United States and sixteen in developing nations.⁴⁵ The total number of women involved in the trials was over 17,000. In the two trials in the United States, the patients in all the study groups had unrestricted access to AZT and other antiretroviral drugs. In fifteen of the sixteen conducted in developing nations, some or all of the patients were not provided with the antiretroviral drugs. Those studies used a placebo control, rather than an active control. In a placebo control, the control group is given a placebo; in an active control, the control group is given the best available proven therapy. The sixteenth trial in developing

⁴³ Peter Lurie and Sidney M. Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *New England Journal of Medicine* 337, no. 12 (1997): 853.

⁴⁴ Shah. *The Body Hunters*, 78-79.

⁴⁵ The trials conducted in developing nations were conducted in Cote d'Ivoire, Uganda, Tanzania, South Africa, Malawi, Thailand, Ethiopia, Burkina Faso, Zimbabwe, Kenya, and the Dominican Republic.

nations was an active-controlled trial (an equivalency study) run in Thailand by Marc Lallmant, a researcher at the Harvard School of Public Health. Lallmant tested three shorter regimes of AZT compared to the full regimen used in the AIDS Clinical Trials Group Study 076. The Harvard study's research question is "Can we reduce the duration of prophylactic [AZT] treatment without increasing the risk of perinatal transmission of HIV, that is, without compromising the demonstrated efficacy of the standard ACTG [AIDS Clinical Trials Group] 076 [AZT] regimen?"

Those using a placebo control argue that the placebo-controlled trials provide the best option for scientifically valid assessment for alternative regimens, and provide the only appropriate research design - answering the question "Is the shorter regimen better than nothing?" Officials and researchers further defend the placebo control by arguing that those patients in the control are being treated at least according to the standard of care in their home country, which consists of unproven regimens or no treatment at all.

Lurie and Wolfe condemn the fifteen placebo controls studies. They argue that the hundreds of infants in the placebo control needlessly contracted HIV. The active control studies, they contend, would yield more useful results without putting infants at risk. Moreover, the standard of care justification is fundamental misunderstanding the concept of standard of care. Lurie and Wolfe maintain that it ought to be based on alternative treatments and previous clinical data, but in developing countries, the standard of care is wrongly based on economically determined policies of governments that cannot afford the drug companies' prices. On those grounds, Lurie and Wolfe argue that the double standard for using a placebo control in developing nations versus the active

control in developed is unethical. They promote developing a single international standard of ethical research.⁴⁶

Marcia Angell supports Lurie and Wolfe's conclusions. She argues that it is only ethical to use placebos when no known effective treatment is available with which to compare a potential new treatment. The justification for the use of placebo controls in those fifteen AZT studies, Angell contends, is reminiscent to those used in the Tuskegee Study of Untreated Syphilis. In the Tuskegee Study, 412 poor African-American men with untreated syphilis were followed and compared to 204 men free of the disease from 1932 to 1972 in order to determine the natural history of syphilis. There were numerous ethical violations in the study. Participants did not provide informed consent. They were also denied the best available treatment.⁴⁷ In the beginning that only meant being denied heavy metal treatment, which was the standard treatment at the time. In the 1930s and early 1940s of the 71 survivors, only about thirty reported receiving some kind of heavy metal treatment.⁴⁸ However, later on penicillin became widely available and was well known to be highly effective against syphilis, but the study continued without providing penicillin to the infected participants. Investigators justified the denial of treatment by arguing that because the participants were poor they would not have been treated anyways. The researchers argued that they were merely observing what would have

⁴⁶ Lurie and Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," 853-856.

⁴⁷ Marcia Angell, "The Ethics of Clinical Research in the Third World," *New England Journal of Medicine* 337, no. 12 (1997): 847-849.

⁴⁸ Susan M. Reverby, "More than Fact and Fiction: Cultural Memory and the Tuskegee Syphilis Study," *The Hastings Center Report*, 31, no. 5 (September - October 2001): 25, accessed April 17, 2013, http://www.thehastingscenter.org/uploadedFiles/Bioethics_Forum/Reverby.pdf.

happened had there been no study at all. That, Angell argues, is very similar to the standard of care justification; “[w]omen in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what would happen to the subjects’ infants if there were no study.”⁴⁹

Lurie, Wolfe, and Angell’s articles were controversially received, particularly by the pharmaceutical industry, and the debate was ignited. They brought light to an ethically gray area of clinical research that had not previously received the attention it deserved. When is it ethical to use a placebo? Is a double standard between research in the developed and developing world ethically justified? Almost twenty years later, progress has been made, but little consensus still exists.

Surfaxin

Respiratory distress syndrome (RDS) is a common disease in premature infants that is potentially fatal. It is caused by insufficient surfactant, a protein fluid that helps enable proper lung inflation and aeration, in the lungs. The standard treatment is surfactant therapy, which has produced a thirty-four percent decrease in neonatal mortality in randomized trials in the Western world. There are four surfactants approved by the FDA since 1990 - Exosurf, Survanta, Infasurf, and Curosurf. Despite the proven reduction, as of 2008, RDS is the fourth leading cause of infant mortality in the United States and is responsible for up to half of all infant mortality in developing countries as they do not have access to surfactant therapy or ventilation support. While surfactant therapy has been approved for use in Latin America, it is too expensive (U.S. \$1,000-

⁴⁹ Angell, “The Ethics of Clinical Research in the Third World,” 847-849.

\$2,400 per child) for it to be a viable option for most infants, where the per capita ranges from U.S. \$60 - \$140.

In 2000, Discovery Labs, a private U.S. drug company, planned a Phase III trial to demonstrate the efficacy of a new surfactant called Surfaxin, and deliberated with the FDA about an acceptable trial design. Initially, Discovery Labs proposed an equivalency study or active-controlled trial comparing Surfaxin to Survanta. While the FDA would have accepted an active-controlled trial comparing Surfaxin to Exosurf as proof of Surfaxin's effectiveness, the FDA, based on previous surfactant studies, did not think a trial of Surfaxin against Survanta would yield data that would support the approval of Surfaxin.

After deliberations, a multi-center, double blind, randomized, two-arm, placebo-controlled trial was proposed, which would involve 650 premature infants with RDS in Bolivia. Half of those infants would be receiving a placebo. The hospitals chosen for the study did not have surfactant therapy available for the treatment of RDS. The sponsor did agree to provide endotracheal tubes, ventilators, and antibiotics for all study participants. A team of American neonatologists was proposed to be sent to supervise the trial and help train local health care personnel. The principal target market for the drug was the U.S. and Europe, but no plan was offered by the sponsor to market in Latin America. There were negotiations between the sponsor and participating hospitals to

make Surfaxin available to them at a reduced cost if it proved efficacious, but no firm agreement was reached.⁵⁰

In 2001, the Public Citizen Health Research Group learned of the proposed Surfaxin trial, and managed to obtain several FDA internal memos. The internal FDA meeting where they discussed the Surfaxin trial was entitled “Use of placebo controls in life-threatening diseases: is the developing world the answer?”⁵¹ That title stirs controversy when combined with one internal memo that Public Citizen obtained where the FDA acknowledged that “conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA.” The FDA documents also state that some hospitals in countries where the study was proposed have access to surfactants, but are completely unavailable at other hospitals.

On February 22, 2001, Public Citizen wrote a letter to Tommy Thompson, Secretary of the US Department of Health and Human Services. The letter contained the following:

[p]articularly because the FDA approved another surfactant (Infasurf) in 1998 on the basis of studies performed between 1991 and 1993 in which all infants were treated with a presumably effective drug and none were given placebo, we call on you to immediately put a stop to plans for this unethical and exploitative study in its present design. The study is unethical because it violates the principle that placebos not be employed when there exists a standard treatment that may reduce or prevent harm, improve health or prolong life. If the study produces findings

⁵⁰ Jennifer S. Hawkins and Ezekiel J. Emanuel, ed., “Case Studies: The Havrix Trial and the Surfaxin Trial,” in *Exploitation and Developing Countries: The Ethics of Clinical Research*, (Princeton: Princeton University Press, 2008), 58-61.

⁵¹ “Request to the Department of Health and Human Services to halt plans for unethical placebo-controlled study of drug for respiratory distress syndrome in Latin America unless it is redesigned to treat all patients,” Public Citizen, <http://www.citizen.org/publications/publicationredirect.cfm?ID=6761>, quoted in Ruth Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge: Cambridge University Press 2004), 17.

that are beneficial to patients in wealthier countries but the drug is not widely available in the countries in which it was tested, an additional dimension of unethical behavior will have been added. For the study to take place ethically, all infants must be provided with a treatment either known or expected to be effective; a comparison of the new surfactant to an already approved one would therefore be acceptable.⁵²

Despite having supporters for the original design, six weeks later, Public Citizen announced that Discovery Labs had redesigned the trial using an active control versus a placebo.⁵³

Double Standards: Placebo-Controlled Trials (PCTs) and Drug Availability

Those two trials highlight two of the most popular ethical complaints on clinical research in developing nation: the use of a PCT and the host nation's lack of availability of the experimental drug should it prove effective. Let us look at each issue in turn.

In both the AZT and the Surfaxin trial, the chief objection was that a placebo control was being used when known effective treatment existed. They were even available on the market for use and purchase in developed countries, specifically the United States and Europe. However, they were not readily available in the country in which the trials were being run or were proposed to be run in.⁵⁴ Thus, while a PCT might be unethical to run in a developed nation where the drug is available, supporters of PCTs argue that it is ethical for those same trials to be run in a developing nation where the

⁵² "Request to the Department of Health and Human Services to halt plans for unethical placebo-controlled study of drug for respiratory distress syndrome in Latin America unless it is redesigned to treat all patients," Public Citizen, <http://www.citizen.org/publications/publicationredirect.cfm?ID=6761>, quoted in Ruth Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge: Cambridge University Press 2004), 18.

⁵³ Macklin, *Double Standards in Medical Research in Developing Countries*, 17-18.

⁵⁴ I shall call the countries in which the trials are being run the host country.

drug is not available. That is, the placebo is not any worse than the no treatment the developing nation participants would be receiving if they were not enrolled in the trial.

There are many reasons I will discuss throughout this dissertation on why the double standard on PCTs is ethically troubling, but one in particular is its violation of equipoise. As Dr. Benjamin Freedman describes equipoise,

[t]here is widespread agreement that ethics requires that each clinical trial begin with an honest null hypothesis. In the simplest model testing a new treatment B on a defined patient population P for which the current accepted treatment is A, it is necessary that the clinical investigator be in a state of genuine uncertainty regarding the comparative merits of treatments A and B for population P. If a physician knows that these treatments are not equivalent, ethics requires that the superior treatment be recommended. . . I call this state of uncertainty about the relative merits of A and B “equipoise.”⁵⁵

Freedman argues that equipoise is ethically necessary in all clinical research, including placebo-controlled trials, and between all arms of a trial, otherwise the trial ought to be designed to exclude the inferior treatment. If equipoise has been disturbed, the trial may have to be terminated with all subjects, both current and previously enrolled, receiving the superior treatment.⁵⁶

Freedman also distinguishes between theoretical and clinical equipoise. Theoretical equipoise, which is conceptually odd and ethically irrelevant, exists when the overall evidence for two alternative treatments is exactly balanced.⁵⁷ Clinical equipoise, which is ethically relevant, exists under the following circumstances:

...there is a current or imminent conflict in the clinical community over what treatment is preferred for patients in a defined population P. The standard treatment is A, but some evidence suggests that B will be superior... Or there is a

⁵⁵ Benjamin Freedman, “Equipoise and the Ethics of Clinical Research,” *New England Journal of Medicine* 317, no. 3 (1987): 141.

⁵⁶ Freedman, “Equipoise and the Ethics of Clinical Research,” 141.

⁵⁷ Freedman, “Equipoise and the Ethics of Clinical Research,” 144.

split in [the] clinical community, with some clinicians favoring A and others favoring B. Each side recognizes that the opposing side has evidence to support its position, yet each still thinks that overall its own view is correct. There exists ... an honest professional disagreement among expert clinicians about the preferred treatment. A clinical trial is instituted with the aim of resolving this dispute.⁵⁸

Given this understanding of clinical equipoise, Freedman proposes the following formal conditions under which a trial may be run ethically:

at the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed. In other words, the results of a successful clinical trial should be convincing enough to resolve the dispute among clinicians.⁵⁹

Under Freedman's account of clinical equipoise, using PCTS in developing nations when an existing treatment exists violates clinical equipoise, as it is already known prior to the trial that the placebo is worse than the standard treatment. As Franklin G. Miller and Howard Brody argue, "[w]hat makes it ethical to conduct [a random-controlled trial] comparing a new treatment with a standard treatment, but not with a placebo, is that experts in the clinical community are uncertain or in a state of disagreement about whether the new treatment is as good as or better than standard therapy."⁶⁰

It is possible for researchers to not violate clinical equipoise in developing nation trials. Researchers can use an active-controlled trial (ACT), where the control group is giving

⁵⁸ Freedman, "Equipoise and the Ethics of Clinical Research," 145.

⁵⁹ Freedman, "Equipoise and the Ethics of Clinical Research," 145.

⁶⁰ Franklin G. Miller and Howard Brody, "What makes placebo-controlled trials unethical?" in *The Ethics and Regulation of Research with Human Subjects*, ed. Carl H. Coleman, Jerry A. Menikoff, Jesse A. Goldner, and Nancy Neveloff Dubler (Newark: LexisNexis, 2005), 262

the standard treatment that exists, assuming that they are uncertain about whether the active control is better or worse than their experimental drug. Lallmant used an ACT, as did Discovery Labs after redesigning the Surfaxin trial.

In chapter 4, I will further engage the equipoise debate and analyze the ethical underpinnings of using PCTs in developing nations. For now, it is only important to understand that there is a double standard regarding PCTs and clinical equipoise for trials in developing nations and trials in developed nations.

The second major ethical critique of clinical trials in developing nations is researchers and pharmaceutical companies not making the experimental drug available to the host nation at an affordable rate should the drug be proven effective. In 2000, the World Health Organization developed Millennium Development Goals (MDG) - goals which they wanted to accomplish by 2015.⁶¹ MDG 8 is to develop a global partnership for development, part of which is to provide access to affordable essential medicines in developing countries in cooperation with pharmaceutical companies. The MDG Gap task force in its recent report found that in the public sector, generic medicines are only available in 38.1% of facilities and cost 250% more on average than the international reference price. In the private sector, those same generic medicines are available at 63.3% of facilities and on average cost 610% more than the international reference price.⁶² In a survey of over 40 mainly low-income and middle-income countries, generic

⁶¹“Millennium Development Goals (MDGS),” World Health Organization, accessed April 17, 2013, http://www.who.int/topics/millennium_development_goals/en/.

⁶²“New UN report confirms ongoing lack of access to essential medicines,” World Health Organization, accessed April 17, 2013, <http://www.who.int/medicines/mdg/en/index.html>.

medicines were only available at 44% of health facilities in the public sector and 65% of health facilities in the private sector.⁶³

With such little drug availability and continuing health problems, developing nations are desperate to have access to low-cost medicines and research. However, as demonstrated in the AZT and Surfaxin case, there is little effort on part of the pharmaceutical companies to provide the tested drug at a reasonable price. Rather, than lowering the price, they test the drug at lower doses to see if it is effective so that they can sell that lower dose at a lower price to developing nations, as was the case with AZT. If the trial takes place in the developed world, drug availability is not an issue as the primary target market for the experimental market is the developed world. This topic, including the feasibility of providing the drugs at lower prices, will be discussed in further detail in chapter 4.

What is particularly disturbing about the use of PCTs and the lack of drug availability is that developing nations are undertaking all the risk while the developed world is the primarily beneficiary from the research which violates the principle of justice in the Belmont Report. As will be discussed in chapter 4, international and U.S. federal guidelines call on researchers to balance the risks and benefits to the patients. Yet, the risk undergone by developing nations is high, especially when a placebo versus an active control is used, with little benefit received from the research or drug availability. Moreover, developed nations have access to the drug and the research from the trial without any of the medical risks associated with the trial. Furthermore, there is not

⁶³ “Median availability of selected generic medicines,” World Health Organization, accessed April 17, 2013, http://who.int/gho/mdg/medicines/availability_text/en/index.html.

strong justification, be it scientific or ethical, for the double standard beyond financial benefit and efficiency on the part of the researchers and pharmaceutical companies.⁶⁴ In other words, developing nations are being exploited as pharmaceutical companies and researchers are using the countries' lack of resources and health needs to gain.

Consent

Though I will not be considering problems with consent within my analysis of exploitation and the double standards in international research, it is a large enough problem to warrant some discussion as part of the background information. In general, be it in a developing nation or developed nation, there are problems with informed consent. In seeking consent, the FDA requires researchers to provide the following basic elements potential participants:⁶⁵

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are

⁶⁴ There is a debate about whether ACTs can provide the same statistical analysis as PCTs. That debate will be analyzed in chapter 4.

⁶⁵ These elements are required for all research requiring informed consent. Depending on the details of the trial, they may require additional elements.

available if injury occurs and, if so what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research- related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.⁶⁶

Few researchers, however, check a patient's understanding of those elements. As

Shah describes,

[f]ew researchers... ever bother to verify whether their subjects do, in fact, understand. It wouldn't be difficult. Medical researchers routinely double-check, duplicate, and re-analyze nearly every other aspect of clinical trials by means of a profusion of journal articles, conferences, workshops, and lectures. "Relentless scrutiny of details" could be said to be the research industry's motto. But in the area of informed consent, an atypical atmosphere of 'don't ask, don't tell' prevails.⁶⁷

In a study published in 2001, while over half of researchers agreed that verifying subjects' understanding of experiments is a good idea, only 16% have done so in their own trials.⁶⁸

Verification is increasingly important as few patients fully read and comprehend informed-consent documents, as they tend to be too long with a difficult degree of readability. In July 2011, a study published in the *Journal of Internal Medicine* reviewed 124 informed-consent forms in 21 HIV clinical trials sponsored by the National Institute of Health's Division of AIDS. It found that the forms were typically written above the

⁶⁶ "A Guide to Informed Consent - Information Sheet," U.S. Food and Drug Administration, accessed April 17, 2013, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>.

⁶⁷ Shah. *The Body Hunters*, 147.

⁶⁸ Shah. *The Body Hunters*, 147.

ninth-grade reading level and were longer than twenty-two pages.⁶⁹ As Nancy Kass, lead author of the study, describes, “[v]ery few people are going to sit down and read a document that’s that long and the goal is to have people understand. The whole reason for putting [informed consent] in writing is with the belief that someone will read it. The longer it is, the less likely people are to read it all the way through, and then you have defeated your own purpose.”⁷⁰

That problem is compounded in developing nations where there is not only potentially language barrier but also a cultural barrier. In many developing nations there is a lack of familiarity or understandings of western medicine, scientific research, and basic concepts of modern science. In a report by the National Bioethics Advisory Commission, analysts point out that in some African languages, not only are there are no words for “science” or “research,” but there is no concept to explain “placebo” or “experiment.” As the same word for “science” is often also used for “medicine,” analysts argue that many adult subjects have no understanding of the difference between being a research subject and receiving medical treatment.⁷¹

Moreover, there are difficulties in getting developing nations subjects to sign the informed consent documents. In a study published in 2001, M Upvall and S Hashwani of Aga Khan University in Pakistan compared informed consent procedures in Pakistan and Swaziland. According to their study, researchers had to jump through many hoops

⁶⁹ Kevin B. O’Reilly, “Informed-consent documents called too long and complex,” *American Medical News*, August 3, 2011, accessed April 17, 2013, <http://www.amednews.com/article/20110803/profession/308039996/8/>.

⁷⁰ Nancy Kass quoted in Kevin B. O’Reilly, “Informed-consent documents called too long and complex,” *American Medical News*, August 3, 2011, accessed April 17, 2013, <http://www.amednews.com/article/20110803/profession/308039996/8/>.

⁷¹ Macklin, *Double Standards in Medical Research in Developing Countries*, 148.

created by tribal hierarchy and corrupted bureaucracy in order to obtain informed consent. At times, they had to ask the husbands of wives or village elders first. Researchers also struggled to contact subjects, as some do not have telephones or permanent addresses. Some are even afraid to sign their names.⁷²

In addition to practical difficulties in obtaining and verifying informed consent, there are several philosophical questions. What constitutes informed consent? Are we respecting patients' autonomy if we are unable to achieve 100% informed consent? If total informed consent is achieved, does that nullify any concern over wrongdoing concerning the double standards in clinical practices between developing and developed nations? This last question represents one of responses to charges of exploitation in developing nations. Some argue that if one consents to the act, it is either not exploitative or the wrongdoing of the transaction is nullified. I argue that even if fully we achieve total informed consent, pharmaceutical companies and researchers are exploiting developing nation participants, and that is harmful to those participants. In chapter 4, I look specifically at the consent justification. As a result, I will not be engaging the consent debate and will assume total informed consent throughout this dissertation.

Why Exploitation?

Exploitation is the correct model for understanding the wrongdoing imposed by pharmaceutical companies and researchers on developing nations for three reasons. First, in a minimal sense, Jennifer S. Hawkins argues that exploitation means to “take advantage” of someone or something. That includes both moralized and non-moralized

⁷² Shah. *The Body Hunters*, 151.

senses of exploitation. In the moralized sense, which is the sense we are concerned with, that interaction of ‘taking advantage’ must be unfair or morally problematic in some sense.⁷³ Based on this minimal sense, pharmaceutical companies and researchers seem to be exploiting developing nation participants in clinical drug trials. They are using the participants’ vulnerable circumstances - lack of access to health care and existing treatment - to offer them less than developed nation participants for the sake of benefit - money, efficiency, etc. One party is benefitting through the use of another. For it to be exploitative, that use must be unfair or morally problematic. It seems unfair, as they are not receiving the same benefits that they would receive if they were living in the developed world. With a minimal depth understanding of exploitation, then, it intuitively seems that clinical trials in developing nations are exploitative.

Second, as Hawkins and Ezekiel J Emanuel argue, exploitation provides a model that unifies many research concerns into a single ethical issue. Those concerns, as discussed, include study design, specifically over the choice of control, drug availability, informed consent, and the balance of risks and benefits for patients.⁷⁴ Though different in consequences, all stem from a single interaction, or rather a single set of interactions, - the drug trial. No matter what form the research takes or where it is located, “all research ‘uses’ the participants to gain information that, hopefully, will improve the health of

⁷³ Jennifer S. Hawkins, “Research Ethics, Developing Countries, and Exploitation: A Primer,” in *Exploitation and Developing Countries: The Ethics of Clinical Research*, ed. Jennifer S. Hawkins and Ezekiel J. Emanuel. (Princeton: Princeton University Press, 2008), 44.

⁷⁴ Jennifer S. Hawkins and Ezekiel J. Emanuel. “Introduction: Why Exploitation?,” in *Exploitation and Developing Countries: The Ethics of Clinical Research*, ed. Jennifer S. Hawkins and Ezekiel J. Emanuel. (Princeton: Princeton University Press, 2008), 10-13.

others whether directly or indirectly through additional research.”⁷⁵ Since all concerns with developing nation clinical research stems from that ‘use,’ it seems natural to categorize them under a single moral umbrella. Exploitation is wide enough to encompass all of those issues. While it is possible to understand each concern as a different moral wrong; however, this only complicates the task of understanding the moral wrong in clinical research, which is both theoretically and practically unattractive if there is to be timely policy changes.

Third, the language of exploitation runs heavily in the clinical trial literature particularly on the topic of developing nations. In their critique of the AZT trial, Lurie and Wolfe state,

[r]esidents of impoverished, postcolonial countries, the majority of whom are people of color, must be protected from potential *exploitation* in research. Otherwise, the abominable state of health care in these countries can be used to justify studies that could never pass ethical muster in the sponsoring country [my italics].⁷⁶

Harold T. Shapiro and Eric M Meslin call for safeguards in clinical research;

[a]n important additional safeguard is needed to avoid the *exploitation* of potentially vulnerable populations in developing countries - namely clinical trials sponsored or regulated by U.S. groups should be limited to those that are responsive to the host country’s health needs [my italics].⁷⁷

George J Annas and Michael A Grodin similarly argue,

unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects developed countries are simply *exploiting* them in order to quickly use the knowledge gained

⁷⁵ Hawkins and Emanuel, “ Introduction: Why Exploitation?,” 12.

⁷⁶ Lurie and Wolfe. “ Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries,” 855.

⁷⁷ Harold T. Shapiro and Eric M. Meslin, “Ethical issues in the design and conduct of clinical trials in developing countries,” *The New England journal of medicine* 345, no. 2 (2001): 139.

from the clinical trials for the developed countries' own benefit. . . . The central issue in doing research with impoverished populations is *exploitation* [my italics].⁷⁸

This language continues throughout the literature. Exploitation is the field's chosen lens through which to view the problems.

While there are benefits, accepting exploitation as the model of moral wrong doing has its negatives. Specifically, exploitation is a diffuse and vague concept. There are moral and non-moral examples of exploitation. For example, to say that an athlete exploits his talent to throw the football farther than anyone else to win a game is to use exploitation in the non-moral sense. That is, the athlete's action is not morally worrisome.⁷⁹ Moreover, there is little agreement as to what constitutes exploitation or why exploitative actions are morally bad.

The double standard in clinical research is particularly troubling for exploitation theories as it appears that patients are better off having been exploited by the trial than they would have been had the trial not taken place. Pharmaceutical companies and researchers make this argument in defense of the double standard. As seen particularly in the AZT case, even with a placebo control patients have a chance of getting the actual experimental drug and will receive medical care, which they would not have had otherwise. It seems as if, on balance, patients are benefiting rather than being harmed.

⁷⁸ George J Annas and Michael A Grodin, "Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa," *American Journal of Public Health* 88 (1998): 560-563 at 561 quoted in Jennifer S. Hawkins and Ezekiel J. Emanuel. "Introduction: Why Exploitation?," in in *Exploitation and Developing Countries: The Ethics of Clinical Research*, ed. Jennifer S. Hawkins and Ezekiel J. Emanuel. (Princeton: Princeton University Press, 2008), 12.

⁷⁹ Hawkins and Emanuel, "Introduction: Why Exploitation?," 13.

Explaining how this instance of exploitation, which seems to be mutually beneficial for both the researchers and the patients, is morally bad. This will be the topic of Chapter 2.

The Remaining Chapters

There are four additional chapters after this one. In “Chapter 2: What is exploitation?” I examine existing theories of exploitation. Specifically, I will look at the theories of Alan Wertheimer, John Lawrence Hill, and Ruth Sample, who offer the best explanations for how exploitation might be mutually beneficial but still be morally wrong. The goal of this chapter is not to discuss why exploitation is harmful, but rather discuss what exploitation is. After discussing why each does not meet the challenge of explaining exploitation of clinical research developing nations, I will offer my own theory. Rather than offering a theory of all exploitation, I will identify and develop a type of exploitation, which I call comparative exploitation. I argue that the double standard in clinical research is an example of comparative exploitation.

In “Chapter 3: How Comparative Exploitation is Harmful” I argue that cases of exploitation that seem to be mutually beneficial, like clinical trials in developing nations, are actually harmful to the victims. I have two main arguments as to why they are actually harmful. First, I argue that the assumption that the victim is benefitting rather than being harmed relies on the standard counterfactual account of harm. I contend that under the standard account, the wrong counterfactual question is being asked when determining if harm occurred. Rather, I rely on Ben Bradley’s account, which changes the counterfactual question to one where harm in comparative exploitation can more easily be understood. Second, I argue that even under the standard counterfactual

account of harm, exploitation that is thought to be mutually beneficial is actually harmful because it creates a climate of harm under which increases the likelihood that the victims will get harmed.

“Chapter 4: Standard of Care” analyzes the standard of care debate. The standard of care argument is one offered by supporters of the double standard in international researcher. They argue that when guidelines say “best therapeutic method available” that means the best available in the host country, not in any country. Thus, they are justified when they use a placebo control in countries where the existing medical alternative is not available in the host country. Within this chapter, I argue against the standard of care response, particularly analyzing the concerns over the use of placebo-controlled trials and the availability of the experimental drug should it prove effective. I contend that the participants from developing nations be treated the same as those in developed nation.

Finally, in “Chapter 5: Conclusion” I will conclude the dissertation and examine one final issue. Alan Wertheimer argues that though clinical research in developing nations may be exploitative, we should allow the exploitation to continue otherwise pharmaceutical companies and researchers will not continue to conduct clinical trials in the developing world. I argue that we cannot allow exploitative drug trials to continue.

Chapter 2: WHAT IS EXPLOITATION?

Introduction

Exploitation theories vary as widely as they are numerous.⁸⁰ Many suggest that exploitation requires that the exploiter has a net gain while the exploited party has a net loss. For example, Allen Buchanan argues that “to exploit a person involves the *harmful, merely instrumental utilization* of him or his capacities, for one’s own advantage or for the sake of one’s own ends.”⁸¹ Judith Farr Tormey contends that “[e]xploitation necessarily involves benefits or gains of some kind to someone... Exploitation resembles a zero-sum game, viz what the exploiter gains, the exploitee loses; or, minimally, for the exploiter to gain, the exploitee must lose.”⁸² The problem with such theories is that there are plenty of cases of exploitation where the exploited party gains overall rather than loses. Consider child labor. Often children are forced to work in factories in order to earn an income for their families. If they do not work they may die of starvation, thus it is to their benefit that they work. Yet, we still maintain that companies who hire child

⁸⁰ Much of the exploitation literature that examines specific moral problems does not discuss the Marxist tradition in depth. I suspect that is because the moral situations discussed do not often fit within an economic framework, and there is a fear that an overarching concept of exploitation would be too vague and unable to fully grasp the moral wrongness. For the sake of narrowing my project and honing in on the specific moral complaints of clinical drug trial, I have decided not to include the Marxist tradition in this chapter. Marxism is not discussed in much of the literature on exploitation in clinical drug trials.

⁸¹ Allen Buchanan quoted in Alan Wertheimer, "Exploitation," *The Stanford Encyclopedia of Philosophy*, edited by Edward N. Zalta, (2008), updated July 24, 2008, <http://plato.stanford.edu/archives/fall2008/entries/exploitation/>.

⁸² Judith Farr Tormey quoted in Alan Wertheimer, "Exploitation," *The Stanford Encyclopedia of Philosophy*, edited by Edward N. Zalta, (2008), updated July 24, 2008, <http://plato.stanford.edu/archives/fall2008/entries/exploitation/>.

laborers are exploiting the children. This type of exploitation, where the exploited party gains, is called mutually advantageous exploitation.

It can be argued that clinical drug trials in developing nations are an example of mutually advantageous exploitation. It is to the participants' benefit to participate in the trial where even though a placebo is used; they have a chance of receiving medication or compensation. If they do not participate, they have zero chance of receiving any kind of treatment. However as in the child labor case, the consensus is that the trial participants are being exploited. An account is needed to explain how these sorts of cases classify as exploitation and what moral wrong is being done to the exploited parties.

In this chapter my goal is to analyze existing accounts of exploitation and then offer my own account. While there are many theories of exploitation, I will only discuss the theories of Alan Wertheimer, John Lawrence Hill, and Ruth Sample. I have chosen those theories for their popularity, plausibility, and for their vastly different approaches to the problem of mutually advantageous exploitation. This chapter will not explore why exploitation is morally wrong, but rather focus on why certain situations are categorized as exploitation.⁸³ While all three approaches offer plausible accounts for exploitation, they fall short in their explanative force of the moral wrong done by the double standards in clinical research. In the introduction I explained why exploitation is the correct framework for the double standards between developed nations and developing nations'

⁸³ As suggested in the Chapter 1, I will argue in Chapter 3 that the victims of exploitation from clinical drug trials are harmed rather than benefitting. Thus, clinical drug trials are mistakenly labeled as mutually advantageous. However, I believe one of the reasons for their mislabeling is because existing theories of exploitation do not adequately explain why the double standard is exploitative. The goal of this chapter is to offer a theory that explains why the double standard in clinical research between developing nations and developed nations is exploitative.

clinical trials, and this chapter will explain why specific theories of exploitation are failing this case. After discussing the obstacles of those three approaches, I will offer my own account. My own account is not a full theory of exploitation, but rather an account of a specific type of exploitation, which I call “comparative exploitation”.

I have made some assumptions that I want to clarify. First, many theories of exploitation including the ones discussed in this chapter argue that if there is a defect in consent then the interaction is exploitative. While defects in consent are a concern for mutually beneficial exploitation, including clinical drug trials as discussed in the introduction, I want to examine the clinical drug trial cases under the best of circumstances. Thus, for the sake of this chapter, I assume no defects in consent for trial participants. Second, in describing the happenings between the exploiter and the exploited party, I will use the words transaction and interaction interchangeably. This terminological use is consistent with what is found in the literature. No deeper meaning is meant by using one word over another. Third, for clarity’s sake through this chapter, I will reference the hypothetical example of A exploits B. Thus when I refer to A, I mean the exploiter, and when I refer to B, I mean the exploited party.

Wertheimer

In an early formulation of exploitation, Wertheimer categorizes a transaction as exploitative if A takes unfair advantage of B. Note that Wertheimer defines exploitation in terms of fairness rather than harm. In doing so, he is able to craft two sub-categories of exploitation: harmful exploitation and mutually advantageous exploitation. In harmful exploitation A gains from a transaction or action that is harmful to B, where harm is

defined in terms of an appropriate baseline; whereas, in mutually advantageous exploitation A unfairly gains or gains in an excessive amount from a transaction that is beneficial to B. Whether A unfairly or excessively gains is determined by the same baseline used in harmful exploitation.⁸⁴ Moreover, in order for a mutually advantageous transaction to be wrongfully exploitative, the outcome must be in some way unfair to B. Wertheimer admits that mutually advantageous exploitation can be understood as a form of harmful exploitation in so far as the transaction is evaluated by reference to a fairness baseline.⁸⁵

Critical to both types of exploitation is that A must gain at least *ex ante*, if not also *ex post*. That is, a transaction cannot be exploitative if A did not at least believe he was going to gain from the transaction prior to actually transacting with B. It may be the case that unforeseen circumstances prevented A from receiving a benefit, but the transaction may still be exploitative.⁸⁶ Suppose a pharmaceutical company exploits me by testing a new drug on me without my consent that has harmful consequences to my health. *Ex ante* the company would have benefited by proving the drug effective and selling it on the market. However, if that new drug does not prove effective and the company chooses to no longer use it (no *ex post* benefit), I have still been exploited by the company. A also need not intend to exploit B in order for A to exploit B. A may exploit B if A thinks the transactions is fair *ex ante* or is unaware of the effects of the transaction on B.⁸⁷ Wertheimer further clarifies that A's gain need not be financial and A

⁸⁴ Alan Wertheimer, *Exploitation* (Princeton: Princeton University Press, 1996), 207.

⁸⁵ Wertheimer, *Exploitation*, 22.

⁸⁶ Wertheimer, *Exploitation*, 209.

⁸⁷ Wertheimer, *Exploitation*, 209.

need not exploit B for personal gain. A could exploit B on behalf of a third party C. This later case, Wertheimer classifies as mediated exploitation.⁸⁸

In order to determine the baseline of fairness for transactions, Wertheimer refers to the Best Alternative to a Negotiated Agreement (BATNA);

[a] party's BATNA is a course of action, for example, to do nothing or to transact with another party. A BATNA has a value to each party. Call it the *reservation value*. With reference to that reservation value, each party determines his or her *reservation price*, a price that is just equal to the reservation value, the minimum threshold value that he or she is prepared to accept for entering into an agreement.⁸⁹

If A receives more than the reservation price, then A has gained from the transaction.⁹⁰

Wertheimer distinguishes between two notions of reservation price: actual reservation price and A's morally justified reservation price. An agent's actual reservation price is a counterfactual in two ways. First, it is the minimum price that the agent would accept, and second, it is a function of the agent's general knowledge of the market and the reservation price of the other agent involved in the transaction.⁹¹ On the other hand, the morally justified reservation price is the baseline used to understand an agent's gain. The morally justified reservation price is often no less than the actual reservation price but it need not be. Wertheimer intends it to be a baseline not a ceiling.⁹²

The morally justified reservation price is the fair price for a transaction. Fairness does not dictate that all of the parties involved in the transaction must gain equally.⁹³

Rather, Wertheimer suggests agents should utilize hypothetical markets to determine fair

⁸⁸ Wertheimer, *Exploitation*, 210.

⁸⁹ Wertheimer, *Exploitation*, 211.

⁹⁰ Wertheimer, *Exploitation*, 211.

⁹¹ Wertheimer, *Exploitation*, 212.

⁹² Wertheimer, *Exploitation*, 211-213.

⁹³ Wertheimer, *Exploitation*, 223.

prices. The hypothetical market price is the “accepted baseline price that was set by a ‘fairly conducted market...in the absence of fraud, monopoly, or coercion.’”⁹⁴

Wertheimer uses the following example to motivate his use of hypothetical market price. Consider two friends, A and B. A wants to sell her house to B and B wants to buy A’s house. Both parties want to transact at a fair price so as to avoid taking unfair advantage of the other. How do A and B determine a fair price of the house? Using Wertheimer’s hypothetical market framework, the two friends should determine the price produced by a fair competitive market.⁹⁵

Wertheimer admits that the hypothetical market model does not inherently reflect a deep principle of justice. However, he finds the model attractive because, as Wertheimer describes,

...it does reflect a crucial moral dimension of the relationship between the parties to the transaction. The competitive market price is a price at which neither party takes *special* unfair advantage of particular defects in the other party’s decision-making capacity or special vulnerabilities in the other party’s situation. It is a price at which the specific parties to this particular transaction do not receive greater value than they would receive if they did not encounter each other. It may or may not be a ‘just price,’ all things considered, but it may well be a nonexploitative price, for neither party takes unfair advantage of the other party.⁹⁶

Moreover in a perfectly competitive market, there are no important differences in bargaining power between A and B. Wertheimer does assume that there is a bargaining range between A and B; “for where there can be no bargaining, there cannot be an

⁹⁴ Wertheimer, *Exploitation*, 231. Wertheimer is quoting Raymond de Roover, “The Concept of the Just Price: Theory and Economic Policy,” *Journal of Economic History* 18, no. 4 (1958): 420-21

⁹⁵ Wertheimer, *Exploitation*, 230.

⁹⁶ Wertheimer, *Exploitation*, 232.

inequality in bargaining power.”⁹⁷ That is, because A and B bargain when it comes to the terms of a transaction, there must be a difference in bargaining power. Although, there is no inequality in bargaining power if A’s and B’s reservation prices are roughly equidistant from the bargain price. Consider the example of B who needs to buy food from A. B may feel an injustice as B is on a tight budget and would like to pay less for food than what A is charging. Similarly, A may have liked to have charged B more for food, but was prevented from doing so by the market. “So,” Wertheimer argues, “despite the fact that there are important objective and phenomenological inequalities between A and B [such as A being a big firm and B being a lowly individual], there is no inequality of bargaining power...”⁹⁸ In other words, because the price that B ended up paying for the food was between the price that B wanted to pay and the price A wanted to charge, there is no inequality in bargaining power according to Wertheimer.

Based on that analysis, Wertheimer believes that to say that B has a bargaining weakness “is simply another way to state that B’s reservation price is higher than some norm or is likely to generate a price that is much greater than the cost to A or what *might* be A’s reservation price in the absence of B’s vulnerability or other competitors.”⁹⁹

Wertheimer goes on to argue that bargaining weakness do not equate an inequality of bargaining power; “vulnerabilities are interactive. Although B’s vulnerability creates opportunities for A, B can use those very opportunities as a lever against A. Once the situation is redefined in this way, there is no obvious inequality of bargaining power

⁹⁷ Wertheimer, *Exploitation*, 266.

⁹⁸ Wertheimer, *Exploitation*, 266.

⁹⁹ Wertheimer, *Exploitation*, 269.

between the parties. . .”¹⁰⁰ What Wertheimer is suggesting is that a transaction is not necessarily exploitative if there is a difference in bargaining power. While I agree that a difference in bargaining power does not necessitate exploitation, if the difference in bargaining power is too great, the transaction can become exploitative. I will further explain that idea in detail further on. Additionally, Wertheimer is vague as to how B can leverage his vulnerabilities against A. In fact, as I will argue, there are situations where B’s vulnerabilities are so great that B has no bargaining power. In those cases, A is easily able to exploit B.

Wertheimer’s explanation of A exploits B if and only if A takes unfair advantage of B, seems intuitively correct, and I accept that part of his argument. However, Wertheimer’s unpacking of “unfair advantage” in terms of a hypothetical competitive market is problematic. Ruth Sample makes that argument. Sample agrees with Wertheimer that exploitation does not necessarily involve harm, coercion, an unequal distribution of the social surplus of an interaction, or unequal bargaining power; however, she disagrees with Wertheimer’s claim that “exploitation occurs when one pays a nonstandard price for the object of a transaction.”¹⁰¹ Such a claim, according to Sample, produces some counterintuitive results. She offers the example of the wealthy tourist visiting a poor nation, where the average daily income is one dollar. Within the market of that nation, the fair value of a pineapple is five cents. The tourist is offered the pineapple for a price of twenty-five cents. Even though the tourist has a hunch that the locals pay a lower price, the tourist buys the pineapple at twenty-five cents. Has the

¹⁰⁰ Wertheimer, *Exploitation*, 269

¹⁰¹ Ruth Sample, *Exploitation, What It Is and Why it is Wrong*, (Lanham: Rowman and Littlefield, 2003), 16.

tourist been exploited? Sample argues that despite paying five times the market value for the pineapple, the tourist has not been morally wronged. She explains,

[e]ven if the vendor earns much more than a subsistence wage - say, five dollars per day - I am inclined not to chastise her for exploitation, but to congratulate her for her enterprising activities, especially when no dishonesty is involved and the transaction is not of a Good Samaritan sort. It simply does not seem generally wrong to charge a nonstandard price for something.¹⁰²

I share Sample's intuition. Perhaps a motivation for that intuition is the inference that the tourist is wealthy and may be from a country where the fair market price of a pineapple is three dollars. If the tourist would generally pay three dollar for a pineapple, it seems odd to say that she has been exploited when paying twenty-five cents. Which market is to govern the fair price of the pineapple, the tourist's home country or the visiting country? If it is the visiting country, then it seems that the tourist should be able to fly in and buy a lifetime supply of pineapples at twenty-five cents and return home with them. She would still be paying five times the fair market value as dictated by the visiting country, but is paying substantially less than the fair market value of the pineapple in her home country. In that scenario, it seems that the tourist is exploiting the pineapple sellers of the visiting country. The tourist could be paying them more but is taking advantage of their need to sell at a price lower than the tourist's home country. If the home country's market is to determine fair value, then consider this example: the tourist actually originates from an even poorer country where the fair market value of pineapples is one cent. Even if the tourist buys the pineapple at market value of the visiting country, five cents, then the tourist would be exploited as he is paying more than the fair value of the pineapple in his home country. Simply put, Wertheimer's analysis of

¹⁰² Sample, *Exploitation, What It Is and Why it is Wrong*, 23.

hypothetical markets to set the baseline for fairness over simplifies a very complex system, which is made even more complicated since wealth varies so greatly between communities.

Moreover, Sample argues that rather than articulating what it is for a transaction to be fair, and then choosing a system, which conveys that fairness, the hypothetical market system seems to be a convention chosen without any regard as to whether it is genuinely fair. She explains,

...it is clear that this is an understanding of exploitation as *failure to adhere to a convention*. It says that in the context of a market for a given object, paying the standard (i.e., normal) price, when there is a competitive market for the object, would make the transaction, *ceteris paribus*, nonexploitative. But why should we accept this? It may be true that the law regards transactions as fair when they meet this standard (hence the doctrine of unconscionable contracts), but that is not the same as showing that they *are* fair and that they do not exploit. Competitive market prices are set by supply and demand, and if a person has a monopoly on a resource - such as employment - this may drive demand and thus prices up.¹⁰³

To illustrate her point, Sample points out the labor situation in the Pacific Rim countries. In that region, laborers outnumber capitalists, so that the market price for labor is relatively low. Many have the intuition that those laborers are being exploited and yet under Wertheimer's account the fair market price is being met.¹⁰⁴

Here is another example to bolster Sample's point. In some of those Pacific Rim countries, children are a part of the work force. The children's wages are necessary in order to keep their families afloat financially, and they are being paid in accordance with what the market in those countries dictates. Both sides in the transaction, the children (along with their families) and the capitalists, are benefitting. Yet we call such factories

¹⁰³ Sample, *Exploitation, What It Is and Why it is Wrong*, 24.

¹⁰⁴ Sample, *Exploitation, What It Is and Why it is Wrong*, 24.

sweat shops, and believe to a very certain degree that those children are being exploited. As Sample explains, Wertheimer's theory cannot account for the exploitation and moral wrong done in those cases.

Both of Sample's points highlight an obstacle with Wertheimer's account. When there are two different fair market prices, how does one determine what is the most fair market value? What reason is there for choosing one price over the other? Without any additional guideline for fairness, any chosen market price would be chosen arbitrarily. Furthermore if an additional principle of fairness for exploitative transactions is needed, why rely on hypothetical markets at all? As Sample points out, Wertheimer has not offered any reasoning as to why hypothetical markets are the best convention for determining fair transactions. Rather hypothetical markets seem to complicate the matter.

The Pacific Rim laborers, particularly the children workers, examples mirror the problem of clinical drug trials in developing nations. Both the researchers and trial participants are gaining after the interaction. The trial participants, like the laborers, are not in a position where they cannot interact. With more laborers than employers, there is a financial strain forcing laborers to accept low paying jobs, and similarly, in many cases trial participants do not have access to any health care. A drug trial is better than no treatment whatsoever. Thus, like the laborers example, the clinical drug trial problem poses problems for Wertheimer's account.

To determine the fairness of the transaction between the researchers and trial participants, according to Wertheimer, "we must measure the fairness of their gains

against a *normative standard* as to how much the parties *ought* to gain.”¹⁰⁵ That normative standard, as discussed, is determined by a hypothetical market. However, that framework does little to offer a standard of fairness for a clinical transaction. First, it suffers from the same criticism as in the pineapple example. Does one use the hypothetical market modeling the conditions of the host country that have virtually no health resources available for the general public or the conditions of the researcher’s country where more medication and health services are available? Second, the interaction between the researchers and the trial participants is not a typical transaction involving commodities. The participants’ bodies, health, and well-being are at the center of the interaction. With such high stakes for the participants, an economic-based concept of hypothetical competitive market does not seem to be the appropriate mechanism for determining fairness.

Wertheimer does recognize the pitfalls of relying on the hypothetical market model and tweaks his theory of exploitation in *Rethinking the Ethics of Clinical Research: Widening the Lens*. His new formulation defines a transaction as exploitative if B receives less from (or pays more for) the interaction than is required by a plausible principle of fairness. Wertheimer admits that he is unable to offer an unproblematic principle of fairness that adequately explains the unfairness of mutually beneficial transactions. Thus, for the sake of argument, he argues, “that some mutually advantageous transactions are unfair by reference to an appropriate normative

¹⁰⁵ Alan Wertheimer, “Exploitation in Clinical Drug Trials.” in *Exploitation and Developing Countries: The Ethics of Clinical Research*. edited by Jennifer Hawkins and Ezekiel J. Emanuel, (Princeton: Princeton University Press, 2008), 73.

standard.”¹⁰⁶ Unfortunately, this new formulation does not solve our earlier problem as to what the normative standard of fairness ought to be for clinical drug trials.

When specifically addressing the exploitative nature of clinical drug trials, Wertheimer does not believe that the critics of the clinical drug trials have proven why the distribution of benefits between the parties is unfair.¹⁰⁷ First, he argues that in some cases, it is unclear who the beneficiaries of the transaction are. In private research, clearly the pharmaceutical companies gain in profit; however, the study could be run by a not-for-profit organization such as the National Institute for Health, in which case the beneficiary is unclear. Wertheimer says that you could claim that the scientists gain, but it seems that the intended indirect beneficiaries of the trial are the trial participants.¹⁰⁸ I agree with Wertheimer. Trial participants are intended indirect beneficiaries, but I would also contend that in both the trials run by private companies and not-for-profit organizations, the community from which the company and organization originate, the developed world, is also an intended beneficiary. After the trial is run, as previously discussed, the developed world gains the majority of benefit over the developing world. Thus, it seems only fair that when considering the distribution of benefits, if we consider the benefits of both parties.

¹⁰⁶ Alan Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 211.

¹⁰⁷ In his assessment of the critics’ arguments, Wertheimer deliberately sets aside the standard of care argument. Wertheimer believes that to be the strongest argument put forward by critics and has a separate solution for standard of care. I will discuss that solution in the standard of care chapter.

¹⁰⁸ Alan Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 226-7.

Second, Wertheimer argues that it is possible to interpret investigators as offering fair *ex ante* packages to trial participants through placebo-controlled trials. Prior to entering the trial, the participants had zero percent chance of receiving beneficial treatment. Those odds increase upon entering the trial. If only half of the participants receive the actual medicine, whereas the other half receive a placebo, the odds for all participants of receiving beneficial treatment has increased from zero to fifty percent. Additionally, even those who are receiving the placebo are receiving all around better care than they would have if they had not entered the trial.¹⁰⁹ While I agree that that the participant does have some *ex ante* benefit from entering the trial, that does not mean that the benefit is fair and thus the overall transaction fair and nonexploitative. Consider the following example: my sister and I do the same amount of chores, but I receive \$10 for my work, but my sister only receives \$5. Even though my sister does receive more benefit, \$5, doing the chores than had she not done the chores and received \$0, her benefit is still unfair as she only received half the amount of money I received for doing the same amount of work.

One might make the following objection. My sister and I are employees of Al. Suppose Al is required by law to pay me twice as much as my sister for the same amount of work. That is, Al is left with two choices; either (A) offer my sister and me \$5 and \$10 respectively or (B) offer us nothing. Also suppose that both my sister and I are better off with option A than B. Under these circumstances, it is not clear that option A is unfair or exploitative. While it is clear that it is unfair to treat those who are alike in all

¹⁰⁹ Alan Wertheimer, Rethinking *the Ethics of Clinical Research: Widening the Lens*, 227.

morally relevant aspects differently when treating them alike is an option, it is far less clear that it is unfair to treat those that are alike in all morally relevant aspects differently when treating them alike is not feasible or if treating them alike makes them better off.¹¹⁰

This objection confuses the source of the unfairness. Even though the law prevents Al from paying my sister and me equal amounts does not mean that the unequal payment is fair. Al is not the source of the unfairness as he does not necessarily intend to be unfair to my sister and me, but rather the law that requires me to receive twice as much is. The law, in treating my sister and me differently when we ought to be treated similarly, is unfair, and thus, every instance of the law being enacted is an unfair example of that law. If we are to place feasibility as a limit on fairness in transactions, the question of fairness becomes more of a practical issue than a normative one.

Additionally, in the cases of mutually beneficial exploitation that I am looking at - clinical drug trials and child labor - there are no strict laws that prevent the exploiter from transaction with the victims in a fair and moral manner. In fact, as was discussed in the introduction and will be examined in further length in chapter 4, for clinical drug trials, the legal standard promotes equal treatment for individuals who are alike in all morally relevant aspects. So while this objection may be of concern for other exploitative situations, it does weigh heavily in this instance.

Third, Wertheimer dismisses the argument that clinical trials in developing nations are exploitative because they serve the interests of the wealthy nations. Citizens of wealthy nations have medical needs. He argues, “the issue is not the legitimacy of the interests that are being served, but whether those who serve those interests are being

¹¹⁰ Objection from Dr. Douglas Portmore

treated fairly.”¹¹¹ For example, if Oriental rug makers were treated fairly, we would not say they are being exploited just because they are providing goods for affluent westerners¹¹². Wertheimer’s example is dis-analogous to the case of clinical drug trials. There is a difference between a person who makes a good and a person who is allowing their body to be tested on for medical purposes. The trial participant is taking on much greater personal risk than the person knitting oriental rugs. For a participant to take on a great risk only to have that benefit wealthy nations versus this own community is an important factor in determining whether the risk for the participant is warranted. Moreover, many participants are unaware that their participation in the trial will not benefit their community as much as wealthy nations. If trial participants believe their community is one of the major intended beneficiaries, then it seems that participants are not fully aware of the terms of the transaction to which they consenting.

Furthermore, understanding wealthy nations as the intended beneficiaries is important to the exploitation debate because of the double standards that exist between the trials run in those wealthy nations and those run in developing nations. If developing nations are serving the interests of wealthy nations, do they not at least deserve the same conditions as the trial participants from those wealthy nations assuming it is feasible to do so? If developing nation participants are only serving the needs of their own community, then one might be able to justify the different standards. But since both trials in developing and developed nations have the same beneficiary, it seems that the terms

¹¹¹ Alan Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 228.

¹¹² Alan Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 228.

should be the same in both cases. This will be discussed in further detail in the chapter on standard of care.¹¹³

Hill

Hill argues that exploitation concerns a psychological disparity rather than an economic or social disparity. Though economic and social inequalities may exist between the two parties involved in an exploitative transaction, it is the psychological vulnerability between the two that qualifies the transaction as exploitative. To demonstrate that intuition, Hill uses the example of a college student who entices her college professor into a sexual relationship for a better grade. While the student has a lower social position, she is exploiting a weakness of the teacher.¹¹⁴

In order for a transaction to be exploitative in the legally relevant sense, according to Hill, the following five conditions must be met. The transaction must,

- 1) consist of an offer of benefit, never a threat
- 2) which is made intentionally, knowingly or recklessly on the part of the offeror, such that it is likely to involve, implicate or take advantage of;
- 3) a psychologically recognized vulnerability or weakness on part of the offeree;
- 4) where the vulnerability or weakness characteristically results in a significant impairment of the rational-emotional capacity of the individual;
- 5) that the offer actually has the effect of impairing the rational-emotional capacity of the offeree;
- 6) such that, but for the impairment of this capacity, the offeree would not have accepted the offer.¹¹⁵

Let us look at each of those conditions in turn. First, the transaction must consist of an offer of benefit, never a threat. This emphasis on benefit over threat serves to

¹¹³ Wertheimer does discuss a couple of other arguments: the difficulties of identifying the beneficiaries and the fairness of off-shoring

¹¹⁴ John Lawrence Hill, "Exploitation," *Cornell Law Review* 79 (1994): 679.

¹¹⁵ Hill, "Exploitation," 683-4.

distinguish exploitation from coercion. Coercion often involves a threat of harm to B if B does not comply with the terms of the transaction. Additionally, Hill notes, that the offer to B need not be objectively beneficial; “many offers are considered exploitative in part precisely because the offer of benefit is illusory.”¹¹⁶

Second, the offer is made intentionally, knowingly or recklessly on the part of the offeror, such that it is likely to involve, implicate or take advantage of. This condition mandates the intent of the offeror to exploit. Hill rightly frames the standard of intent objectively rather than subjectively. That is there are two criteria for intent: “the offeror must act voluntarily and the act must be performed with the desire to, or with substantial certainty that the act will in fact bring about some specific consequence.”¹¹⁷ Hill also quite rightly includes cases of recklessness where A was in a position to have the consequences of his interaction with B and should have known them before engaging in the interaction. Concerning the latter half of the statement, “likely to involve, implicate or take advantage of,” Hill does not mean that A must necessarily create a cognitive impairment (though his definition of exploitation does encompass those cases), but A may merely take advantage of a pre-existing condition. That is,

the offeror must subjectively know, or there must be substantial certainty, given what the offeror knows or should know about the offeree’s situation, that the offer will undermine the rational capacities of the offeree. The offeror must, therefore, act in conscious disregard of the likelihood of exploitation.¹¹⁸

Third, the offeror is taking advantage of a psychologically recognized vulnerability or weakness on part of the offeree. By vulnerability Hill means, “a

¹¹⁶ Hill, “Exploitation,” 684.

¹¹⁷ Hill, “Exploitation,” 684-685.

¹¹⁸ Hill, “Exploitation,” 685.

disposition of personality or circumstance of life that serves to hamper the rational-emotive process, such as severe depression, grief, guilt, fear or physiological addiction.”¹¹⁹ Key to Hill’s notion of vulnerability is their resulting in an internal psychological state that interferes with one’s reasoning processes. There are several situations that do not necessarily but can result in vulnerabilities, such as poverty, political oppression or social alienation. While Hill recognizes that it can be difficult to determine when said situations create a vulnerability, what is important for his concept is that vulnerability require more than “mere credulity, gullibility, curiosity, or naiveté.”¹²⁰

Hill’s explanation for vulnerability is unsatisfying. If theorists are unable to clearly identify the circumstances under which B’s circumstances in life create a vulnerability, then to what extent can we hold A accountable for knowledge of B’s vulnerability? I am not suggesting there are not cases of exploitation where A did not intentionally exploit B but recklessly engaged in the transaction. However, A’s epistemic burden seems too high given the gray area Hill portrays. Rather than simplifying exploitation’s complexities, Hill has shifted the complexity to the concept of vulnerability.

Fourth, the vulnerability or weakness characteristically results in a significant impairment of the rational-emotional capacity of the individual. In order to prove that volitional states can affect one’s ability to reason, Hill looks at three different types of examples. First, volitional states affect beliefs. Consider a man drowning in a lake with no hope of rescue. The only thing within reach that may help him is a piece of straw.

¹¹⁹ Hill, “Exploitation,” 686.

¹²⁰ Hill, “Exploitation,” 687-688.

Under normal circumstances, that man believes a piece of straw is not strong enough to support his weight and allow him to pull himself ashore. However, under his current circumstances, Hill argues, it would not be surprising to find the man grasping at that straw to try to prevent his drowning. That is because the man's fear of death and drowning merits his trying to use the straw to save himself, or as Hill argues given the circumstances the man now has the belief, as improbable as it may be, that the straw might save him.¹²¹

Volitional states also affect one's values. Consider the example of a person who values property rights. That person believes that it is immoral to steal. However, if that person were starving or was unable to feed her children, she would very likely steal food in order to feed herself and/or her children. While in other circumstances, upon seeing a loaf of bread, said person may reason that it is wrong to steal, so I will not steal the bread. However, in a situation in which she is starving, her values may change, and she may reason that it is not wrong to steal the bread because I am starving. This shows a change in her reason due to a change in her values originating from a volitional state.¹²²

Finally, volitional states affect one's behavior. He appeals to people's erratic behavior during times of emergency. Often times when an emergency arises, such as a burning building, a person choking, etc., some people panic and do not act rationally. The emergency circumstances affect one's ability to reason and act accordingly, such as calling 911.¹²³ Despite his examples, Hill admits the practical difficulty of giving a full account of the psychological analysis of rational decision-making. Rather, he relies on

¹²¹ Hill, "Exploitation," 675-676.

¹²² Hill, "Exploitation," 677.

¹²³ Hill, "Exploitation," 678.

tort law in suggesting that “a particular decision will be deemed “rational” if it would be made by a reasonable person in the subject’s circumstances.”¹²⁴ Thus, if a person acts differently than a reasonable person would, the person is not acting rationally.

While Hill is able to offer examples of ways in which volitional states can affect our rationality, I have the same worry as explained under the third condition. Hill does not offer a full enough account that would allow A to determine if B is vulnerable and if that vulnerability is affecting B’s decision-making. If we rely on his “reasonable man standard,” I am still at a loss as to what characteristics define the reasonable man, and to what extent A should have knowledge of what a reasonable man is. Furthermore, what if it is unclear what the reasonable man would do? Often on controversial issues, such as stem cell research and clinical drug trials, it is unclear what the reasonable action is. Consider the following scenario: A and a bystander C disagree on what the reasonable man would do. A thinks B is acting reasonably and C does not. Thus A thinks he is not exploiting B but C thinks he is. How are we to determine who is correct? If we are to accept Hill’s account of exploitation, we must develop clearer standards for what it means to act rationally in a given situation.

Let us look at the fifth and sixth conditions together. The fifth condition is that the offer actually has the effect of impairing the rational-emotional capacity of the offeree, and the sixth is that but for the impairment of this capacity, the offeree would not have accepted the offer. Important to note that from those conditions we can rule out cases where A intends to exploit B but there is no actual effect. Exploitation requires A actually influencing B, and B acting in a way that would be different from how they

¹²⁴ Hill, “Exploitation,” 689.

would have acted without cognitive impairment. It is also important to notice that Hill's account does not discuss B's position after the interaction. That is, B could be left better off after the transaction and still have been exploited.¹²⁵

Hill's theory does effectively account for some exploitative scenarios that other theorists, such as Wertheimer, cannot. Consider the following case: a dance studio convinces a lonely, depressed widow she has dance talent and should purchase \$50,000 worth of dance lessons. In order to pay for the lessons, she must sell everything she owns, including her home.¹²⁶ Has the widow been exploited? Perhaps, she is not being charged a higher price than any other dance and was pursued to the same degree that any other potential dance student would be. Given those conditions, Wertheimer's theory struggles to classify this situation as exploitative. However, intuitively, it seems that the dance studio is exploiting the widow. Hill's account has the explanative force behind that intuition. Because she is depressed and lonely, the widow is psychologically vulnerable, which is affecting her rational decision-making processes. The dance studio is taking advantage of that psychological vulnerability whether it be intentional or recklessly when they allow her to sell all of her belongings and spend \$50,000 on dance lessons. Had she not been depressed and lonely, the widow may not have made the same decision.

How might Hill, then, explain the intuition of exploitation in clinical drug trials? If pharmaceutical companies are exploiting the developing world participants, it is because the participants are psychologically vulnerable which is interfering with their

¹²⁵ Hill, "Exploitation," 689-690.

¹²⁶ Hill, "Exploitation," 631.

ability to rationally consent to participation in the trial. That psychological vulnerability arises from their lower socioeconomic position. That is, because the participants are poorer without access to healthcare, their desire for medical care overrides their rationality in deciding to enter a trial. However, if we believe the participants to be rationally consenting to the trial, then a psychological vulnerability is not interfering with their decision-making processes, which means, according to Hill they are not being exploited.

While Hill's account may have weight with cases like the dance studio and widow, I reject that idea that in order for a transaction to be exploitative, the exploited party's rationality must be called into question. There are several instances of exploitation where it seems that the exploited party, B, has entered into the transaction rationally. Let us say that B is dying of dehydration and will die within the hour if he does not drink a glass of water. A, who is not dying of dehydration, has a glass of water and will give B the glass of water for \$20. B, having \$20, buys the glass of water from A and lives. A has clearly taken advantage of B's situation in order to make \$20. Does this mean B had a psychological vulnerability that created a psychological disability, which affected his ability to rationally make a decision? No. There is no evidence that B has psychological disability. Rather it seems that B was acting quite rationally. If B did not pay \$20 for the glass of water and died, many would think that B would have been acting irrationally. One's life is surely worth more than \$20. The situation is similar for clinical drug trials. Given a choice between no health care and perhaps certain death or entering a trial that offers a chance of a survival, though the conditions of the trial may not be

optimal, it seems that the rational decision would be to enter the trial. However, that rational consent does not dismiss the exploitative nature of the trials.

Sample

Rather than appealing to fairness, Sample places lack of respect at the center of exploitation. She argues that exploitation “involves interacting with another being for the sake of advantage in a way that degrades or fails to respect the inherent value in that being.”¹²⁷ The consequences of that disrespect are connected to the exploitative act but need not be constitutive of it. That is, while some exploitative acts are harmful in and of themselves, exploitation may also be mutually beneficial.¹²⁸

Sample identifies three broad categories for ways in which we may disrespect a person’s value. We fail to respect a person by (1) neglecting what is necessary for that person’s well-being or flourishing, (2) taking advantage of an injustice done to him, and (3) commodifying an aspect of that person’s being that ought not be commodified. In each category, there is a lack of respect for human value that motivates the charge of exploitation.¹²⁹

Similar to other theorists, Sample believes that A must gain from the transaction with B in order for the transaction to be exploitative. A need not have intent to exploit for the act to be exploitative. Sample observes three ways in which exploitation may be unintentional: A may believe that B is not deserving of respect; A may be mistaken about what respect requires; and A may be mistaken in what it takes to fulfill a requirement of

¹²⁷ Sample, *Exploitation, What It Is and Why it is Wrong*, 57.

¹²⁸ Sample, *Exploitation, What It Is and Why it is Wrong*, 57.

¹²⁹ Sample, *Exploitation, What It Is and Why it is Wrong*, 57-58.

respect. In other words, even if A either has mistaken beliefs or is ignorant of what it takes to respect an individual, she can still be held morally responsible for exploiting B.¹³⁰

Sample, also, pays particular attention to cases of exploitation where the transaction is the best available option to B and A is not obligated to interact with B.¹³¹ In such cases, Sample argues that B is vulnerable to A, and that vulnerability takes the form of need. By need, Sample means “not only those objects necessary for physical survival, but also conditions of purposeful employment, the prerequisites of psychological well-being, and constraints on interaction that are necessary for self-respect.”¹³² When A exploits B under those circumstances, A is using B’s need for the sake of advantage in a way that fails to respect B. Though the needs of others do not automatically obligate us to provide for them, Sample argues that the needs of others do constrain how we interact with them. That is, “[i]f we can interact with persons so that their basic needs are taken into account through the transaction, we ought to.”¹³³ If, for whatever reason, the mutually beneficial transaction is unable to provide for those needs, the transaction is not exploitative.¹³⁴

According to Sample’s theory, pharmaceutical drug companies are exploiting trial participants because if they are in a position to provide for the participants’ basic needs, particularly medical care, then drug companies ought to provide for those needs. That is,

¹³⁰ Sample, *Exploitation, What It Is and Why it is Wrong*, 58-59.

¹³¹ As discussed prior, this accurately describes the predicament of clinical drug trial participants and child workers.

¹³² Sample, *Exploitation, What It Is and Why it is Wrong*, 74.

¹³³ Sample, *Exploitation, What It Is and Why it is Wrong*, 75.

¹³⁴ Sample, *Exploitation, What It Is and Why it is Wrong*, 75.

they should make available the drugs on the market in developed nations through active control trials and provide the tested drug at an affordable rate if the trial is successful. Those two items serve to provide for the trial participants health needs. To not do so, under Sample's lens, is to treat the trial participants for the sake of advantage in a way that is degrading to their inherent value.

Sample's account is successful in identifying one way in which mutually beneficial exploitative transactions are morally wrong. They disrespect and/or degrade a person's inherent value. Her theory is particularly apt in cases of interpersonal exploitation. Consider the following scenario: *A* and *B* are parents of a child. *A* and *B* know that grandparents *C* and *D*, having paid for *A*'s college tuition, will not allow the child to go without a college education. *A* and *B* also know that *C* and *D* have enough sayings to pay for the child's college tuition, though they may need to give up some retirement activities. *A* and *B*, thus, decide to spend their savings on traveling rather than saving up for their child's education.¹³⁵ Because relationships vary in character and complexity, finding a standard by which to gauge fairness is difficult. It also seems that in paying for the college tuition, the grandparents are acting rationally toward the child who is in need of education. Yet the scenario seems to leave a morally bad taste in one's mouth. Sample is able to characterize the moral wrongness of the college tuition example. She asserts,

[t]he parents *A* and *B* ... are taking advantage of the family ties of the grandparents *C* and *D*, whose love of their grandchild ensures that they will make tremendous sacrifices to see that the child is educated. Their morally praiseworthy sentimental attachment is a vulnerability that is being used to the advantage of the parents, to the detriment of the grandparents' financial well-being. It is degrading

¹³⁵ Sample, *Exploitation, What It Is and Why it is Wrong*, 8-9.

to have one's generosity not only go unreciprocated, but be preyed upon. It cheapens the value of intimacy to use it in this way.¹³⁶

However, her account seems to blur the lines between exploitation and other forms of wrong doing, which in turn complicates the exploitation debate.

Like many other philosophers, including Wertheimer and Hill, Sample defines exploitation using the phrase "taking advantage." When A exploits B, A is takes advantage of B. It is unclear what that phrase entails. The Oxford English Dictionary defines to take (the) advantage as "to take an opportunity provided by favourable circumstances; to avail oneself of a person or thing. Freq. in negative sense: to seize an opportunity of unfairly profiting by a person or thing, esp. sexually." The latter portion of the definition seems to be what philosophers are intending. However, "to seize an opportunity of unfairly profiting by a person or thing" is too broad of a phrase. That is, we cannot use that phrase to define exploitation as other harms that are not exploitative are encompassed by it.¹³⁷

Consider the sexual connotation of to take advantage of. To say that A takes advantage of B sexually, usually connotes some form of rape. It is easy to see how when A rapes B, A is seizing an opportunity of unfairly profiting by a person or a thing. A seized an opportunity to gain power and pleasure through unfair treatment of B.¹³⁸ While

¹³⁶ Sample, *Exploitation, What It Is and Why it is Wrong*, 90.

¹³⁷ Wertheimer and Hill narrow that field with their extended definitions; Wertheimer references a fairness baseline and Hill makes use of psychological vulnerabilities. Though both formulations inadequately handle some cases of exploitation, they are both successful in narrowing the field of wrongdoing. Sample's definition is not as successful.

¹³⁸ I am interpreting profit to mean more than monetary gain. The Oxford English Dictionary defines profit in many ways, but the way that seems most consistent with cases of exploitation is "a favourable circumstance or condition; advantage, gain; a person's benefit or good."

A did harm B, it would seem odd in this situation to say that A exploited B.¹³⁹ A similar situation arises when examining other forms of wrongdoing. If A and B are business partners and A murders B in order to keep B's share of the profits, clearly A has unfairly profited by killing B, an act which is degrading to B's value, but would we say that A has exploited B?¹⁴⁰ Even if A is serial killer and murders B for the sheer thrill of killing, it is reasonable to describe A as unfairly profiting, in the form of personal pleasure, from killing B, an act which degrades B's value. But yet again, that seems to suggest under Sample's perspective that murder is a case of exploitation.

One could simply bite the bullet and accept that such a broad interpretation of exploitation demands that some harmful acts be considered exploitation that otherwise may not seem to be exploitation.¹⁴¹ I question whether in doing so we are not fundamentally misunderstanding the nature of exploitation as a unique harm, which requires tailored policies to prevent. More practically, a wide notion of exploitation complicates the establishment of laws and standards to prevent exploitation. For example, pharmaceutical companies have utilized the vagueness of the phrase "best proven prophylactic, therapeutic, and diagnostic method available" in the Declaration of

¹³⁹ Perhaps you could say that A exploited a weakness of B if B was not paying attention to her surroundings, or that A exploited the situation, a woman walking alone down an empty street. However than the act of exploitation would be the using of the situation or of the weakness that consequently ended in rape, not the act of rape. I am suggesting that the actual act of rape from which a rapist could profit is an act of exploitation.

¹⁴⁰ Note that A's gain is only unfair in that he is the source of B's death. Had B died of natural causes and had no family who could inherit his business, A as the sole business owner would be entitled to B's share of the profits. So in this scenario, it is not the case that A is exploiting B's death by withholding profits from family members.

¹⁴¹ In conversation Allen would has admitted and accepts that under his view of exploitation, certain cases of murder would be considered exploitation. See: Wood, A., 1995, "Exploitation," *Social Philosophy and Policy*, 12: 136–58.

Helsinki to justify the use of a placebo when a known effective treatment exists. That issue will be discussed in further detail in the standard of care chapter.

Exploitation in Clinical Drug Trials

Each of the three theories is better able to account for some difficult cases of exploitation but not all. Wertheimer successfully explains the exploitative natures of transactions where clear standards of fairness exist. For example, the tow company who charges a stranded motorist \$100 more than fair market value because he is the only tow company available to help. Hill's theory gives explanative force to cases where A treats B no differently than he might treat any other person in the same circumstances but an error in B's judgment during the transaction triggers a charge of exploitation. Recall the case of the dance studio convincing a widow to spend \$50,000 on dance lessons. Sample captures the moral wrongness of exploitation that does not seem overtly harmful or unfair such as in interpersonal exploitation between two family members. However, no one theory is fully able to account for all categories and instances in which we apply the label of exploitation. Perhaps the difficulty with achieving a single overarching concept of exploitation is that the contexts in which we use the word "exploit" vary widely. Joel Feinberg makes that variation apparent in his breakdown of exploitation. At the broadest category, exploitation has two senses: non-pejorative and pejorative. Non-pejorative exploitation refers to opportunities and resources, such as to take advantage of a talent or of an environmental resource. In this sense, the exploiter is always a person. Pejorative exploitation refers to a kind of injustice and moral evil. It involves "a relation between

two or more persons or groups, and ... can involve morally altered relationships among three or even four parties.”¹⁴² .

Feinberg further breaks down pejorative exploitation into coercive and non-coercive. Coercive exploitation is when A forces B to act in a way that is beneficial to A, and non-coercive exploitation is when A takes advantage of B’s traits or circumstances to gain either with B’s consent or without regard to B’s choice at all.¹⁴³ From both the coercive and non-coercive categories, Feinberg identifies nine cases of wrongful exploitation: coercive forcing deceiving, or manipulating-the-incompetent; unequal contest; freeloading and similar cheating; manipulated benevolence; petard-boisting; unproductive cashing in; pandering; harmless parasitism and passive unjust enrichment.¹⁴⁴

I am neither agreeing nor disagreeing with Feinberg’s categorization, though I do find it to be the most complete in the literature. I am merely demonstrating the breadth of cases that fall under the exploitation umbrella. If simply identifying the ways in which we use the term exploitation is so complex, the task of connecting them in a single unified theory is even more daunting. I am inclined to think that maybe exploitation’s wide range is in part due to our erroneously using the same word to describe different types of wrongdoing. That is, the moral wrongness of a painter who charges a couple double for painting the outside of their house because he knows that the couple is extremely wealthy does not seem to be of the same type of moral wrongness when

¹⁴² Joel Feinberg, *Harmless Wrongdoing* (Oxford: Oxford University Press, 1988), 176-177

¹⁴³ Feinberg, *Harmless Wrongdoing*, 178.

¹⁴⁴ Feinberg, *Harmless Wrongdoing*, 206-209.

pharmaceutical drug companies knowingly use different ethical standards for trial participants in developing nations in order to put their drugs on the market faster and at higher prices. How akin is the college tuition case of exploitation to companies hiring children overseas so that they may pay lower wages?

Moreover, no existing theory adequately accounts for exploitation in clinical drug trials. As a result, policy standards remain vague on what constitutes exploitation, which allows pharmaceutical companies to find loopholes and justify inadequate treatment of its trial participants. In order to provide a practical theoretical background from which policy can be drawn, my goal is not to offer a single unified theory of exploitation. Rather I offer a concept of exploitation tailored to the wrongness of clinical drug trials in developing nations. My concept shall be a type or subset of exploitation, which I call comparative exploitation. To offer an analogy, if exploitation were a tree, comparative exploitation would be a branch on that tree. There is a common thread or family resemblance between the types of exploitation, but I am not trying to identify what that thread is. I merely want to fully develop a theory of my one branch.

I suggest looking at the harm done in clinical drug trials and child labor through a comparative lens. When we say A exploits B, it must be possible for A to not exploit B. Moreover, the question of what it is for A to not exploit B may be proven empirically. Maybe A has interacted in the same manner with another person C on another occasion, and that interaction was not exploitative. When an empirical comparison is not available, the question becomes theoretical. We could imagine what a nonexploitative interaction between A and B would look like given some moral framework. If we were unable to find either an empirical or theoretical alternative where A is able to interact with B, or

someone like B, in a nonexploitative matter, that would mean it would be logically impossible for A to not exploit B. Since it is impossible for A to act otherwise, then we would not be able to hold A morally culpable for her actions. However, we hold exploiters accountable for their actions all the time, which means we presuppose that A could have acted differently. Perhaps the key to understanding some types of exploitation is by comparing A's exploitative interaction with A's empirical or theoretical nonexploitative interaction.

Given that comparative lens, I propose the following necessary conditions for comparative exploitation: A exploits B in interaction I if

1. A does x to B in interaction I; and
2. there is a possible world in which C exists such that (1) B and C ought to be treated equally; (2) if A and C engage in I under similar circumstances, A does not do x to C; and (3) it is feasible for A to not do x to B.¹⁴⁵

This is not intended to be a sufficient definition of comparative exploitation. I am merely identifying necessary conditions.

In more difficult cases of identifying the exact reasons why the interaction between A and B is exploitative, it may be easier to identify C and the differences between the two interactions. The addition of (1) under 2 is in order to ensure that the interactions between B and C are alike and ought to be treated alike. If B and C ought not to be treated equally than some of the differences in A's actions towards B and C may

¹⁴⁵ It is possible that B and C are the same person. In an empirical comparison, A and B might have had the same kind of interaction but it was nonexploitative. We could thus compare the current exploitative interaction with the nonexploitative one. In a theoretical comparison, we might use an nonexploitative interaction between A and B's counterparts on a near possible world.

be morally justified and not be reasons why the interaction with B is exploitative. I want to isolate the exact differences that make a nonexploitative interaction exploitative.

Moreover, C in many cases exists in the actual world. However, as suggested, if a theoretical comparison is made then C exists in a near possible world. Suppose some god-like creature enslaves and exploits the entire human race and does not interact with anyone else but the human race. While there is not a being with whom the god-like creature interacts with in a nonexploitative way, we can conceive of what such an interaction would be like, and identify the differences between that interaction and the one between the creature and humans. Then we can determine what humans deserve in order to achieve a nonexploitative interaction with the creature.

Furthermore, the addition of (3) under 2 is to rule out cases where it not possible for A to not do x. That is, on every possible world A does x. For example, it may be the case that on every possible world where her character and dispositions remain the same that my mom pays me twice as much as my sister to do chores. Thus, it is not possible for her to not to do. This example would not be a case of comparative exploitation as it fails (3), though it may be exploitation of a different kind. Recall that I am not offering a theory of exploitation in total, but rather offering a theory of a specific subset of exploitation.

For clinical drug trials, the C is the trial participants in the developed world. As described in the last section, much of the charge of exploitation arises from the double standards between trials in developed versus developing countries. That is, in developing nations, pharmaceutical companies unnecessarily use placebo-controlled trials versus active control, and do not share the benefits of research, such as selling the new drug at

an affordable rate. Those are required of pharmaceutical companies in developed countries.

Trial participants in developed nations are also C because the developed world is the primary intended beneficiary if the trial drug proves successful. Favorable risk-benefit ratio is a common ethical requirement in many clinical trial doctrines including: the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and the Council for International Organizations of Medical Sciences guidelines.¹⁴⁶ The requirement, as summarized by Ezekiel J. Emanuel, David Wendler, and Christine Grady, states, “[clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks.”¹⁴⁷ Pharmaceutical companies are violating the third condition in developing nations. Trial participants are taking on all the risk and receiving very few benefits, which developed nations receive. If those taking on the risk are being exploited and those gaining the benefits are profiting, it seems natural to ask what the interaction would look like if those benefiting took on the risks. That is the ideal situation as proposed by the favorable risk-benefit ratio. Hence why the developed nation seems to be the appropriate C of comparison.

¹⁴⁶ Ezekiel J. Emanuel, David Wendler, and Christine Grady, "What makes clinical research ethical?," *JAMA: the journal of the American Medical Association* 283, no. 20 (2000): 2702.

¹⁴⁷ Emanuel, Wendler, and Grady, "What makes clinical research ethical?," 2705.

Thus, the pharmaceutical companies are exploiting participants in developing nations because they are treating them unequally as compared to participants from developed nations. Note that I am assuming (1) - that trial participants from both nations ought to be treated equally. Pharmaceutical companies argue just the opposite; they ought not to be treated equally because they are not like cases. That is at the core of the standard of care debate and will be discussed at length in a later chapter. For the sake of argument, allow me the assumption of (1) for now.

I am not trying to argue that clinical drug trials even in the most optimal conditions available through the current standards in developed nations are not exploitative. It could be the case that trial participants in developed nations are also being exploited. Maybe it is the case that in order for a participant to not be exploited, they must be written a \$1 million check, which they are currently not receiving. Under those conditions, if the disparity between trials in developed and developing trials did not exist, all participants in all locations would be exploited because they are not receiving that check. That is a different kind of exploitation than the one I am identifying. The type I am identifying, which I will call comparative exploitation, derives from the unequal treatment of like cases for the sake of benefit. Put another way, if A exploits B in interaction I, then A treats B less equally than A has treated, treats, or would treat C in interaction I for the sake of benefit.

Combined with the first formulation, I offer the following definition of comparative exploitation: A exploits B in interaction I iff

1. A does x to B in interaction I; and

2. there is a possible world in which C exists such that (1) B and C ought to be treated equally; (2) if A and C engage in I under similar circumstances, A does not do x to C; (3) it is feasible for A to not do x to B; and
3. A treats B less equally than A has treated, treats, or would treat C in interaction I for the sake of benefit.

Comparative exploitation can also explain other situations. Consider the case of Bob and his two employees Mary and Susan. Mary and Susan have the same type of position at the same level and make the same amount of money. Mary, however, is able to do twice the amount of work as Susan. Bob, knowing that Mary is the more reliable employee, gives Mary twice as much work as Susan. This often leads Mary to working longer hours than Susan, but Mary is not paid any more than Susan even though it is feasible for Bob to do so. Since Bob has Mary doing twice the amount of work as Susan, he does not need to hire a third employee to pick up the slack, which saves him money. Intuitively, it seems that Bob is exploiting Mary and her work ethic.

Comparative exploitation can explain why Bob is exploiting Mary. Let us consider condition 1: there is a possible world in which C exists such that (1) B and C ought to be treated equally; (2) if A and C engage in I under similar circumstances, A does not do x to C; (3) it is feasible for A to not do x to B, then A exploits B. A is Bob. B is Mary, and Susan is C. As Mary and Susan have the same type of position at the same level, they ought to be treated equally, which satisfies (1). (2) is satisfied since Bob interacts as a boss the same way as he does Mary, and yet he is not exploiting Susan. (3) is stipulated in the example; Bob does have the financial means to pay Susan more.

Condition 2 states A treats B less equally than A has treated, treats, or would treat C in interaction I for the sake of benefit. Bob is treating Mary less equally than Susan since he gives Mary more work, and he benefits from doing so by saving money. Both conditions are met. We now have a clearer picture of why the interaction between Bob and Mary is exploitative.

There are other instances of comparative exploitation including some child labor situations and Wertheimer's example of a slave owner who treats two slaves the same but one slave, who is able to do more work, seems exploited over the other.¹⁴⁸ I am not trying to give an exhaustive list of such cases, but rather offer theoretical model for classifying more difficult examples.

Conclusion

In this chapter I have argued that the exploitation theories offered by Wertheimer, Hill, and Sample are unable to account for why the clinical trial double standards between developing and developed nations are exploitative. Rather than offering a full account of exploitation, I have identified a type or subset of exploitation, which I call comparative exploitation. Comparative exploitation is able to explain why the double standards in clinical research are exploitative. In the next chapter, I will explain why comparative exploitation is harmful.

¹⁴⁸ Wertheimer, *Exploitation*, 214.

Chapter 3: How Comparative Exploitation is Harmful

Introduction

In the last chapter, I offered a definition for a specific type of exploitation, comparative exploitation, which relies on unequal treatment for the sake of benefit. Comparative exploitation provides the explanatory force behind claims of exploitation in clinical drug trials in developing nations. In this chapter I will explore the moral wrongness of comparative exploitation. A majority of the literature frames moral wrongness in terms of harm the exploitee suffers. That framework provides a unique challenge not only for some cases of comparative exploitation but more generally cases of mutually beneficial exploitation. In cases labeled as mutually beneficial exploitation, both the exploiter and exploitee seem to be left better off than they would have been had the exploitative interaction not occurred. However, in this chapter I will argue that those cases are not mutually beneficial and the exploitees are actually being harmed in those cases.¹⁴⁹

Rather than creating a new framework with which to evaluate the moral wrongness of comparative exploitation, I will engage the harm debate. In place of arguing for the correct or best harm theory, my goal is to adapt the harm framework found in the clinical drug trials literature to account for harm in comparative exploitation. The harm framework most found in the literature is the counterfactual comparison

¹⁴⁹ Though I argue that the cases referred to in the literature as mutually beneficial exploitation are harmful rather than beneficial, I will continue to use the phrase “mutually beneficial exploitation” to distinguish this group of cases from other cases of exploitation.

account of harm. That is, an action or research is harmful if it leaves the patient or subject worse off than they would have been had the action or research not taken place. The first part of the chapter argues that the traditional counterfactual comparison should be rejected in favor of an alternative counterfactual comparison as argued for by Ben Bradley. First, I will lay out the traditional counterfactual account of harm as explained by Matthew Hanser, Hanser's objections to that theory, and explain how under this model mutually beneficial exploitation does not seem harmful. Second, I will explore an alternative concept of the counterfactual account of harm as constructed by Bradley. I will then explain how Bradley's account successfully answers Hanser's objections. Finally, I will use Bradley's account to explain how mutually beneficial exploitation, particularly mutually beneficial comparative exploitation, is harmful.

The second half of this chapter focuses on how mutually beneficial comparative exploitation can still be viewed as harmful even under the traditional counterfactual account. To accomplish that, I rely on Larry May's notion of shared responsibility. After describing his theory and its application to racist attitudes, I will argue that acts of exploitation, even if they are mutually beneficial, create of a climate of harm that increases the likelihood that the exploited party will be exploited again which in turn increases their chances of being harmed.

As a reminder, PCT continues to refer to placebo-controlled drug trials, A refers to the exploiter, B the exploitee, and C refers to the person A interacts with nonexploitatively.

Harm and Counterfactual Questions

Comparative exploitation cases that are mutually beneficial do not seem harmful as the victim benefits more than they would have had the exploitative interaction not occurred. Consider the proposed Surfaxin drug trial. One can argue that all participating infants, including those who would receive the placebo, benefit from such a trial. As Thomas Pogge writes,

one might even say that *all* infants enrolled in the study benefit, because they all have their survival prospects boosted by a 50 percent chance of receiving Surfaxin treatment. In this way the Surfaxin trial is like a compulsory public vaccination program. Even if such a program causes medical complications for a few children each year, it does save thousands of lives by preventing epidemics. Assuming it is not known which children will suffer complications, the program can be justified to all children on the ground that it improves the health prospects of each. Participation in the vaccination program is in each child's best interest *ex ante*. And so is enrollment in the Surfaxin trial.¹⁵⁰

The comparison being made in this passage by Pogge is between the consequences of the infants being enrolled in the study with the consequences of not enrolling in the trial.

Examining the potential consequences of the interaction having not taken place is a counterfactual question and is often the basis for determining if harm occurs. Such a method assumes a state-based account of harm. That is, "to suffer harm is to be put into (or is perhaps simply to be in) a certain sort of bad state or condition."¹⁵¹ Many state-based accounts are comparative, where to suffer a harm is "to be put into a certain sort of

¹⁵⁰ Thomas Pogge, "Testing Our Drugs on the Poor Abroad," in *Exploitation and Developing Countries: The Ethics of Clinical Research*, edited by Jennifer Hawkins and Ezekiel J. Emanuel (Princeton: Princeton University Press, 2008), 106.

¹⁵¹ Matthew Hanser, "The Metaphysics of Harm," *Philosophy and Phenomenological Research* 22, no. 7, (2008): 421.

comparatively bad state - a state that is *worse* for one than some relevant alternative state.”¹⁵²

One such comparative account is the counterfactual comparison: “to suffer a harm is to come to be worse off than one otherwise would have been.”¹⁵³ In clinical drug trials, such as in the Surfaxin trial, one could make the argument that the patients in developing nations are not being harmed because they are better off than they would have been had the trial not taken place. For example, in the AZT trials, the chance of receiving the lower dose of AZT and not being placed in the placebo control group, no matter how low the probability, is better than not entering the trial and having zero chance of receiving medication. Matthew Hanser analyzes the counterfactual account of harm, and ultimately, dismisses it as the appropriate lens through which to view harm. In an effort to be charitable to counterfactual account defenders, Hanser provides the following formulation of the counterfactual comparison of harm: “a person suffers harm if and only if there occurs an event *e* such that had *e* not occurred he would have been better off in some respect *for some interval of time*.”¹⁵⁴ Hanser adds the phrase “in some respect” in order to avoid the following counter example: a soldier in war loses his foot, but in doing so he avoids losing both of his arms. The counterfactual account might say that the soldier was not harmed because had he not lost his foot, he would have lost both arms. However, the losing of a foot is still a harm. Thus by adding “in some respect” we

¹⁵² Hanser “The Metaphysics of Harm,” 421.

¹⁵³ Hanser “The Metaphysics of Harm,” 422.

¹⁵⁴ Hanser “The Metaphysics of Harm,” 424.

can say that the soldier would have been better off with respect to his foot had the event that took his foot not occurred.¹⁵⁵

Additionally, Hanser adds “for some interval of time” to that construction of the counterfactual account to avoid the six million dollar man counterexample. On the fictional television show *The Six Million Dollar Man*, the title character shatters his legs in an accident, and is given ‘bionic’ replacements that function better than his original legs ever could. While the six million dollar man suffers a tremendous amount to begin with, eventually he is actually better off than he was originally. Does this mean that he was not harmed by the event that caused him to lose his legs? No, he was in fact worse off for an interval of time, hence the addition of the phrase.¹⁵⁶

Under this conception, it seems that mutually beneficial comparative exploitation is not harmful. Particularly for clinical drug trials, often times the alternative to entering the trial is no treatment whatsoever. Had the infants not entered into the Surfaxin drug trial, they would have been worse off as they would not have had a fifty-percent increase in survival. At no interval of time would the infants have been better off had the drug trial not occurred because any chance of treatment is better than guaranteed zero treatment. Additionally, in no respect do they seem to be made worse off.

There are reasons, however, to reject the counterfactual comparison account of harm. Hanser identifies several problems with the counterfactual comparison theory. I will focus on two of his arguments. First, consider preemptive harms. Imagine the following scenario: George wants to burglarize Fred’s store. George thinks that the

¹⁵⁵ Hanser “The Metaphysics of Harm,” 424.

¹⁵⁶ Hanser “The Metaphysics of Harm,” 424.

burglary will go more smoothly if Fred is not there. George decides to go to Fred's house and break his legs so that Fred cannot go to the store the next day. As soon as George gets to Fred's house he finds that Fred's legs have already been broken by Fred's loan shark. According to the counterfactual account, the loan shark did not harm Fred because had he not broken Fred's legs then George surely would have. Thus, as Hanser contends there is no event such that Fred would have been better off had it not occurred.¹⁵⁷

However, it does seem that the loan shark did harm Fred.

Hanser does offer a potential revision for the counterfactual supporter. Perhaps, we ought to compare the world where the loan shark breaks Fred's leg with a world where the loan shark does not break Fred's leg and no relevantly similar event takes place. The new construction is written as "someone suffers harm if and only if there occurs an event such that he would have been better off, for some period of time and in some respect, had neither that event nor any relevantly similar event occurred."¹⁵⁸

However, this new account is still problematic. We are now saying that Fred suffered a harm because he would have been better off had *both* the loan shark not broken his legs and George not set out to break his legs. From the comparative standpoint, it is both of those factors taken together that come to Fred as a harm. However as Hanser points out, that seems wrong, as the loan shark and George did not *jointly* harm Fred. Only the loan shark harmed Fred. Thus, it seems that even the revised counterfactual account misidentifies the harm done to Fred.¹⁵⁹

¹⁵⁷ Hanser "The Metaphysics of Harm," 34.

¹⁵⁸ Hanser "The Metaphysics of Harm," 435.

¹⁵⁹ Hanser "The Metaphysics of Harm," 436.

Hanser's second problem with the counterfactual account is the excessive multiplication of harms. Suppose that Claire shoots Harry, which paralyzes Harry from the waist down. Hanser argues that there is a series of casual events within this action: Claire pulls the trigger, the gun goes off, the bullet enters Harry's body, and Harry becomes paralyzed. According to the counterfactual account, Harry is in a distinct harmed state relative to each of those events. That is, "he is worse off than he would have been had [Claire] not pulled the trigger; he is worse off than he would have been had the gun not gone off; he is worse off than he would have been had the bullet not entered his body; and he is worse off than he would have been had he not become paralyzed. Each of these events, then, comes to him as a separate harm."¹⁶⁰ This seems to be the wrong way to describe the situation for Hanser. There are not four distinct harms, but one harm with several causal antecedents. An acceptable theory of harm, according to Hanser, ought to be to isolate harms from their causal antecedents.

Ben Bradley: A different Counterfactual theory

While the counterfactual comparison theory seems weak given Hanser's objections, Ben Bradley's construction strengthens the position and, I believe, answers Hanser's objections. Bradley argues that in order to understand the value of an action, whether it be of good or of bad value, we appeal to what would have happened if it had not been obtained. That appeal relies on the counterfactual conditional: "if X were to

¹⁶⁰ Hanser "The Metaphysics of Harm," 433.

have happened, Y would have happened.”¹⁶¹ Because of philosophers such as David Lewis and Robert Stalnaker, we, often, interpret those counterfactual conditionals by relying on notions of possible worlds. “According to this view,” Bradley writes, “to say that if X were to have happened, Y would have happened is to say that at the closest possible world in which X happens, Y happens.”¹⁶² In determining closeness of possible worlds, Bradley adopts Lewis’ theory that closeness is determined by similarity. That is, one possible world is closer to the actual world than another possible world if it is more similar to the actual world. Moreover, Bradley thinks of possible worlds as a complete story about the universe: a maximally consistent set of propositions. As he describes,

[t]here is one such story corresponding to the actual world; the story it tells is the story of the actual history of our whole universe from beginning to end. But there are many alternative stories. Some of these are similar to the actual story in certain respects. The most similar world where X does not happen must differ from ours not only with respect to whether X happens, but also with respect to the *consequences* of X’s happening or not.¹⁶³

To demonstrate this similarity relation, Bradley uses the example of Lee Harvey Oswald shooting JFK. The closest possible world where Oswald does not shoot JFK does not go on like the actual world did after the shooting, and it is also not a world where instead of being shot, at the exact same moment JFK suddenly dies of a devastating head injury even for no reason. That latter world is fundamentally not like the actual world because in the actual world no one suddenly gets a devastating head injury for no reason. Rather, Bradley argues, “the closest world is a world where he proceeds along in the motorcade waving to the spectators... (and alternative historians tell us what happens

¹⁶¹ Ben Bradley, *Well-being and Death*, (Oxford: Oxford University Press, 2009), Kindle edition, 48.

¹⁶² Bradley, *Well-being and Death*, 48.

¹⁶³ Bradley, *Well-being and Death*, 49.

after that).”¹⁶⁴ Thus, the closest possible world to the actual world had an event not happened has a great many things different from the actual world.

Identifying the closest possible world is not always a determinate matter. It can depend, as Bradley notes, on what features of the actual world we wish to keep fixed or on a similarity relation of our choosing. Furthermore, if we want to know what the closest possible world looks like had an event not occurred, must that closest possible world be exactly like the actual world right up until the event occurs? Or, can some of the history before the event occurs be different? Bradley considers the example of a woman dying at time *t* after a year-long struggle with cancer. What is the closest possible world where she does not die at time *t*? There are several choices we might choose, including: a world where she dies the next day, a world where she did not get cancer a year ago, a world where her cancer had gone into remission, or a world where she was completely cured. If we hold the past fixed, the first option of a world where she dies the next day would most likely be the closest possible world; however, any of the others are possibilities if we allow the past to vary. Before we can determine “what would have happened” we must decide what should stay fixed and what should vary.¹⁶⁵

Returning to value of an action, recall that Bradley argues that in order to determine the value of an action for a person we compare how things actually went for that person and compare that with how things would have gone had that event not happened. Based on his interpretation of counterfactuals, that means comparing the actual world to the closest possible world where the event did not occur. Given that the

¹⁶⁴ Bradley, *Well-being and Death*, 49.

¹⁶⁵ Bradley, *Well-being and Death*, 49-50.

closest possible world depends on the similarity relation of our choosing, then the value of an action must also be relativized to that similarity relation.¹⁶⁶ From this analysis,

Bradley offers the following principle

Difference-Making Principle (DMP): The value of event E, for person S, at world w , relative to similarity relation R = the intrinsic value of w for S, minus the intrinsic value for S of the most R-similar world to w where E does not occur.¹⁶⁷

Recognizing the close relationship between badness of an event and a concept of harm, Bradley creates a version of DMP for harm, which he calls the Difference-Making Principle of Harm (DMPH). Bradley states, “I am inclined to say that something is bad for a person if and only if it harms her; thus an event harms a person if and only if it makes things go worse for that person that they would have gone otherwise.”¹⁶⁸ I suspect that Bradley intends the formulation of DMPH to be something like this:

Difference-Making Principle of Harm (DMPH): Event E is harmful for person S at world w , relative to similarity relation R, if the intrinsic value of w for S is worse or less than the intrinsic value for S of the most R-similar world to w where E does not occur.

Bradley’s conception of the counterfactual comparison of harm solves for Hanser’s objections

Preemptive Harm

Recall that Hanser’s preemptive harm objection concerns cases where the consequences to the victim seem inevitable even if the event had not occurred, the case of George, Fred, and Fred’s loan shark. Bradley believes DMP can solve for such scenarios.

¹⁶⁶ Bradley, *Well-being and Death*, 50.

¹⁶⁷ Bradley, *Well-being and Death*, 50.

¹⁶⁸ Bradley, *Well-being and Death*, 65.

He considers the case of the young pedestrian. A young man absentmindedly steps off the curb into the path of a bus, and is killed instantly and painlessly. During his autopsy, it is discovered that the young man had a cerebral aneurysm that would have burst within the week and killed the young man had he not been killed by the bus.¹⁶⁹

As Hanser would argue, it seems that DMP would entail that the young pedestrian's death was not very bad for him as he was deprived of very little life. What world is the most similar possible world in which the young pedestrian does not die at that exact moment, t_i ? Bradley states, "[t]ypically, it is a world in which the past as of t_1 (or shortly before t_i) is completely similar to the actual past as of t_i , so that if he had not died at t_i , he would still have died of an aneurysm shortly after t_1 anyway. To suppose that he would not have had an aneurysm in the first place would be to make a gratuitous historical change."¹⁷⁰

However, not all changes of the past before the young pedestrian's death are gratuitous. Bradley considers possible answers to the question, "was the young pedestrian's death at t_1 bad?" Answer #1 is yes; it was very bad. Because he was a young man at t_1 he would have been better off dying at a much later time. Answer # 2 is yes, but it was not very bad. That is because he would have died within a week anyways from an aneurysm. Both of these answers, along with many others, could be correct depending on the context, according to Bradley. While we might initially feel a pull to Answer #1 right after the young pedestrian's death, after the autopsy, we may feel a pull

¹⁶⁹ Bradley, *Well-being and Death*, 52-53.

¹⁷⁰ Bradley, *Well-being and Death*, 53.

to Answer #2. However, it is still possible for us to feel a stronger pull to Answer #1 after the autopsy.¹⁷¹

Bradley contends that our feeling pulled in different directions is because of the vagueness of the question. We can have different comparisons in the mind at the same time, which correspond to different similarity relations. The world that is most similar to the actual world where the young pedestrian does not die at t_i could be several possible worlds. Sometimes it is the world where he dies only a week later, but sometimes it may be the one where he dies a long time after t_i , even if that means some ‘backtracking’ counterfactuals come out true (e.g. had he not died at t_i , he would not have had an aneurysm before t_i). Answer #2 may be the right answer if we are asking if the young pedestrian’s death at t_i was bad for him given that he had an aneurysm. In that context, we are using a similarity relation that counts facts about the very recent past as being very important in determining similarity. This answer emphasizes the *cause* of death. Answer #1 may be right if we are asking if it was bad for young pedestrian’s to die at t_i rather than in old age. In that context, the similarity relation does not count facts about the recent past as important. The closest possible world is one in which he dies much later. This answer emphasizes the *timing* of death. Traditionally, we are more concerned with the timing of death versus the cause of death when determining how bad someone’s death is. Thus, when determining the closet possible world, we do not care if the past events remained fixed because doing so would requires us to fix the cause of death.¹⁷²

¹⁷¹ Bradley, *Well-being and Death*, 53-54.

¹⁷² Bradley, *Well-being and Death*, 54-55.

Let us return to George, Fred, and Fred's loan shark. When Hanser argues that Fred's loan shark did not harm Fred because had the loan shark not broken Fred's leg, George surely would have, he is relying on one type of similarity relation. That is, Hanser assumes that the closest possible world is one in which the past is held fixed. As Bradley points out, adopting that similarity relation emphasizes the cause of Fred's injury versus the timing. Another closest possible world could be one in which the past is not held fixed, and we assume in that world neither the loan shark nor George harm Fred. Hanser argues that to change the past is to change the question. He argues that to take both the loan shark and George's actions into account seems to suppose that they are jointly harming Fred. However, I think Bradley is right. Hanser is placing the emphasis on the cause of the bad thing that happened to Fred, which is only one similarity relation. He is asking the question, "was it bad for the loan shark to break Fred's leg, given that George was going to break Fred's leg thirty minutes later?" One could also ask the question "was it bad for Fred to have his leg broken versus not having it broken at all?" At the very least there seems no reason to prefer Hanser's question over my question. Though, as Bradley argued in the case of death, it does seem that when we are wondering if Fred was harmed, it does not seem that the emphasis is on the cause of that harm, but rather the fact that the harm happened at all. That is, the importance of Fred being harmed seems to be that his leg is broken not so much who broke it. Thus, it seems reasonable to suppose that my counterfactual question relies on the preferred similarity relation versus Hanser's.

Multiplication of Harms

Hanser argued that the counterfactual account interprets a single harm as multiple distinct events and thus multiple distinct harms. Just as in preemptive harm, I think Hanser is relying on a similarity relation that emphasizes cause. Recall that in the case of Claire shooting Harry, Hanser identified four distinct events: Claire pulls the trigger, the gun goes off, the bullet enters Harry's body, and Harry becomes paralyzed. If Hanser considers those four distinct events that cause four distinct states of harm, then there must be four counterfactual questions.

1. Was it bad for Harry that Claire pulled the trigger?
2. Was it bad for Harry that the gun went off given that Claire pulled the trigger?
3. Was it bad for Harry that the bullet entered Harry's body given that Claire pulled the trigger and the gun went off?
4. Was it bad for Harry that he became paralyzed given that Claire pulled the trigger, the gun went off, and the bullet entered his body?

Each of these counterfactual questions assumes a similarity relation that holds the past fixed, which in turn emphasizes the cause of the harm. That is, he assumes, for example, that the closest possible world in which Harry did not get paralyzed may be the one in which Claire did pull the trigger, the gun went off, the bullet entered his body, but it did not paralyze him. Hanser wants an account that isolates the harm from their causal antecedents. That can be achieved through Ben Bradley's account with a different similarity relation.

Suppose we ask "was it bad for Harry that he was paralyzed by a bullet rather than living a longer life free of paralysis?" This counterfactual question emphasizes the

timing of the event. That is, the closest possible world is one in which either Harry is not paralyzed or is not paralyzed until several years down the road. That closest possible world does not hold the past fixed, meaning that some of the “backtracking” counterfactuals come out true. For example, had Harry not been paralyzed, then the bullet would not have entered his body before paralyzing him. Because the past need not be fixed, there is no reason to assume that each of those four distinct events need happen in the closest possible world, which means we can isolate the harm done to Harry from the causal antecedents.

Beneficial Harm

One additional problem for counterfactual accounts is instances where a person is harmed without being made worse off. Bradley considers two cases. First, a woman is raped, becomes pregnant, and raises the child. Even with taking into account the trauma of the rape, the woman’s life is better due to the value of her relationship with her child than it would have been had she not been raped. Second, a man is imprisoned in a Nazi concentration camp. During his time in the camp, the man’s understanding of life is deepened and his character is deepened, so much so that his overall life was better off than it would have been had he not been imprisoned in the camp. Both are cases that seem to involve harm, but it is stipulated that both individuals are better off as a result of the harm. Based on DMPH neither of those two cases seem to be a harm since the victims are left better off than they would have been had the event not occurred.¹⁷³

¹⁷³ Bradley, *Well-being and Death*, 65-66.

To solve this problem, Bradley distinguishes between two different types of harm: all-things-considered and prima facie. All-things-considered harms are harms that are bad for a person taking into account all the harm's consequences for the person. DMPH is that kind of harm. Prima facie harms, on the other hand, are harms that are bad for a person in one way, but may be good for a person in another. Bradley endorses the following account of prima facie harm, which he calls PFH: "[s]omething is a prima facie harm for a person if and only if either (i) it is intrinsically bad for that person, or (ii) it brings about something intrinsically bad for that person, or (iii) it prevents something intrinsically good for that person."¹⁷⁴ The rape victim and Nazi prisoner suffer harm according to PFH but not DMPH. Even though the harm inflicted on the rape victim and Nazi prisoner is not all-things-considered harm does not mean that the perpetrators did not do anything wrong to the rape victim and the Nazi prisoner or that the perpetrators do not deserve punishment for their actions. The perpetrators certainly tried to commit an all-things-considered harm, and also committed prima facie harm against the will and without the consent of the victims. The rights of the victims were also certainly violated. Bradley argues that any of those facts could be grounds for saying the actions committed in those two cases is wrong. Thus, it is false to say that an action is wrong only if it causes an all-things-considered harm.¹⁷⁵

¹⁷⁴ Bradley, *Well-being and Death*, 66.

¹⁷⁵ Bradley, *Well-being and Death*, 66-67.

Comparative Exploitation as an All-Things-Considered Harm

Changing the Counterfactual Question

Let us return to the Surfaxin drug trial case. Would the infants in the trial be harmed? If we understand the question through Hanser's construction of counterfactual harm, then the answer seems to be no. That is, because the closest possible world is one in which the past is held fixed for the infants but the trial never takes places. Since in the actual world with the trial the infants' chances of receiving treatment are boosted by 50% whereas there is 0% chance of receiving medication in the closest possible world where the trial does not take place, the actual world is preferable to the closest possible, which means the infants are not harmed.

In order for cases comparative exploitation to be harmful, then, the exploitee must be left worse off all-things-considered than they would have been had the exploitative transaction not taken place. Note that under that view it does not matter how much less A (the exploiter) offers B (the exploited party) than C (the unexploited interactor with A), so long as B ends up better than she would have had A not interacted with her, B is not being harmed.

However, as I have described, Bradley argues that Hanser's construction assumes the closest possible world is one in which the past is fixed is only one kind of similarity relation, one which emphasizes the cause of the harm. That is, the important fact to remain constant in the closest possible world is one in which A is the cause of said harmful interaction versus some other individual under some other scenario. In the

surfaxin example, by holding the past constant, the emphasis is on Discovery Labs being the interactor with the potential trial participants.

Other similarity relations do exist which place the emphasis elsewhere. Another closest possible world is one in which the transaction between A and B is not exploitative. Perhaps B is offered the same conditions as C or is in a position such that they will receive the same conditions as C. For example, a closest possible world for the Surfaxin trial could be one in which the Brazilian children receive the same benefits that a child of a developed nation would have had the trial been run in a developed nation. Another closest possible world is one in which the Brazilian children do live in a developed nation rather than a developed and as a result of their country's economic standing do receive the same benefits as any other developed nation participant.

At the very least, under Bradley's framework, there is no reason to prefer the past-fixed possible world over the two possible worlds I have suggested. They simply rely on different similarity relations. That being said, it seems that one of the two possible worlds I have suggested are preferable to one that holds the past fixed. *A* being the cause of the exploitative transaction, versus some other potential actor, seems less important as to whether B is suffering a harm than the actual *transaction* between A and B. In other words, what makes a transaction exploitative is not the specific individuals involved, but rather the details and terms of the transaction. For example, Margaret sells Billy a house. Billy is particularly not well informed about the housing market. Margaret, having lots of knowledge about the value of her house and being aware of Billy's lack of housing market knowledge, charges him \$50,000 more than the house's market worth. Margaret has clearly exploited Billy. However, what makes that transaction exploitative is not that

Margaret exploited Billy, for surely if any other individual had done as Margaret had, the transaction would still be exploitative. Rather, it is the terms of the transaction, that the house was unfairly sold at too high of a price, that make it exploitative.

If the root of what makes a transaction exploitative is the transaction itself, or the terms of the transaction, then it seems only natural in determining whether the transaction is harmful, the emphasis should be placed on the transaction. Thus, it seems that the appropriate comparison is between the exploitative transaction and the same transaction conducted nonexploitatively. That is, the closest possible world to the actual world that we should use is one in which A transacts with B but does not exploit B. The counterfactual question would look something like the following: “Was B harmed in the exploitative transaction with A given that A could have transacted nonexploitatively with B?” In the cases that are often thought to be mutually beneficial exploitation, B is not receiving the benefits that he would have received had A transacted nonexploitatively with B. Because B is being denied a benefit in the actual world that she would have received in the closest possible world where A transacted nonexploitatively with B, B is being harmed.

For comparative exploitation, to understand what the nonexploitative transaction with B may look like, we need only look to A’s interaction with C, which as stipulated in the definition of comparative exploitation as nonexploitative. The counterfactual question may look something like “was B harmed in the exploitative transaction with A, given that B should have received the same terms as C?” Thus, any benefits that B did not receive in his transaction with A that C did receive or would have received had she had the same transaction with A counts as a harm to B.

For clinical drug trials in developing nations, the comparison for harm for participants should not be the consequences of the trial occurring versus the trial not occurring, but rather the consequences of the trial run under its current terms versus the consequences of the trial run with the terms offered in developed nations. Primarily, as described in the introductory chapter, the two main items that trial participants and host nations are not receiving is availability of the current market drug through an active-controlled trial (versus a placebo-controlled) and access to the drug being tested at an affordable price once it passed through the FDA and is available on the market. Because researchers are preventing trial participants from receiving those additional benefits, which they would have received had they lived in a developed nation, those participants are being harmed

Given this new counterfactual framework, let us look once again at the surfaxin trial. When determining if the infants in the proposed Surfaxin trial would be hurt, rather than comparing the consequences of the trial to the consequences of not having the trial, we ought to compare the consequences of the trial with the consequences of the trial if it were to be run nonexploitatively. As described in the last chapter, the appropriate C's for clinical drug trials run in developing nations are trial participants in the developed world. That means we ought to compare the consequences of the Surfaxin trial with the consequences of that trial being run in the developed world. The counterfactual question may be like the following: “would the infants be harmed in the clinical drug trial, given that they ought to receive the same terms as potential participants in developed nations?” Since the proposed Surfaxin trial would use a placebo, which would not be allowed in the developed world for ethical reasons, the infants are being harmed. That is, the

appropriate comparison is not a 50% chance of receiving the experimental drug (and not a placebo) versus 0% if the trial does not occur, rather the comparison ought to be a 50% chance of receiving the experimental drug (and not a placebo) versus 100% chance of receiving medication be it existing market medication or the new experimental drug. Thus, because the infants are not receiving the benefits that they ought to be (an increased chance of medication), they are being harmed.

Creating a Climate of Harm

Even if we do not adopt Bradley's framework for the counterfactual question, comparative exploitation can still be harmful all-things-considered with the traditional counterfactual question. That is, it is more harmful for B to engage in a comparatively exploitative transaction with A than to not interact with A at all. The source of that harm lies in the harmful attitudes A projects when engaging in an exploitative interaction with B, and the effect that has on other members in A's social group.

In his book *Shared Responsibility*, May analyzes the relationship between harm, harmful attitudes, those responsible for harm, and groups. He writes

[t]he kind of behavior we engage in does not arise overnight but is normally a function of many successive layers of choosing over the course of a life. For this reason, responsibility is not confined to those isolated actions which have effects on others, but also includes those decisions that form the self into the kind of agent it is and that influence the way that self then acts in the world.¹⁷⁶

Thus, to understand the domain of responsibility, one must understand agency and how one's identity is created. May conceives of agency in terms of social existentialism.

¹⁷⁶ Larry May, *Shared Responsibility* (Chicago: The University of Chicago Press, 1992), 17.

That is, May “stresses the way that our choices are greatly affected by the groups of which we are members.”¹⁷⁷ The attitudes and actions of one’s community influence one’s sense of identity and agency. Likewise, the attitudes and actions one contributes to the community affect the identity and agency of others. Because of the relationship between groups and attitudes, May identifies three cases where responsibility for a harm should be shared by each member of a group and not one single member. The case I am concerned with is where a person does not cause harm, but increases the likelihood that harm will occur.¹⁷⁸

May argues that harmful attitudes can lead to an increased likelihood of harm. For example a parent might have a careless attitude towards his child’s safety. Such an attitude may lead the parent to drive a car in an area where his child is playing, thereby increasing the child’s likelihood of being hit by a car. The careless attitude could also increase the risk of harm by others. The careless parent might omit various precautions, such as removing a rusty nail from the child’s play area, which results in an increased likelihood of the child harming herself.¹⁷⁹

Other such harmful attitudes include risk takers. Risk takers share in the responsibility for a harm their behavior may cause, even though they may not directly cause it.¹⁸⁰ For example, Bob and Tom both drink alcohol and drive afterwards. One night Tom hits and kills Mary, a pedestrian, while driving home drunk from the bar. May

¹⁷⁷ May, *Shared Responsibility*, 16.

¹⁷⁸ May, *Shared Responsibility*, 39.

¹⁷⁹ May, *Shared Responsibility*, 46.

¹⁸⁰ May, *Shared Responsibility*, 43. These are often referred to in the literature as cases of moral luck.

considers Bob to be partially responsible for Mary's death because he engages in the same risk taking behavior.

May offers two reasons why risk takers like Bob are responsible for harms they did not directly cause. First, May argues that the agent who merely risks harm, Bob, and the agent who did in fact cause harm, Tom, act in morally similar ways. May elaborates, "[w]hen two people both have increased the likelihood of harm and both are equally knowledgeable that their actions increased the likelihood of harm, then their risky behavior creates a greater likelihood than previously existed that harm will occur, and they should share in the responsibility for the harms that result."¹⁸¹ Second, risk takers contribute to a climate of risk and/or harm which makes harm more likely to occur.

In order to motivate the argument that an agent is morally responsible for contributing to a climate of risk, May needs to connect harmful attitudes and behavior. Harmful attitudes, for May, are not just mere thoughts or cognitive states. They are also "affective states in which a person is, under normal circumstances, moved to behave in various ways as a result of having a particular attitude."¹⁸² May justifies this claim by asserting that when one wants to test an agent for a particular attitude, the test is behavior, or involves some counterfactual behavioral analysis.

May chooses to focus on racism as the prime example of attitudes that create an environment or climate of harm. Racist agents are risk takers concerning racial violence.

¹⁸¹ May, *Shared Responsibility*, 45. This first reason of acting in morally similar ways does seem a little weak and requires more explanation, which May does not offer in the remainder of his book. However, his model of shared responsibility in cases of risk does not weigh heavily of this reason. In my opinion, the strength of May's argument rests on his second reason of increasing the climate of risk.

¹⁸² May, *Shared Responsibility*, 46.

His aim is to show that “the members of a community who share racist attitudes also share in responsibility for racially motivated harms produced by some of the members because of this climate of racist attitudes.”¹⁸³ That is, the production of racist attitudes is similar to a joint venture. No single person can create a climate in which harm is likely.

Moreover, May argues that those agents who hold racist attitudes but do not harm directly participate in racial harms in society in two ways. First, they causally contribute to the production of racial violence by others. They do this by contributing to a climate “that influences others to cause harm.”¹⁸⁴ May looks to the example of Thomas Becket, the archbishop of Canterbury, and King Henry II as evidence. Henry II’s knights killed Becket after “the king created a climate of opinion simply by asking aloud why he had no followers loyal enough to rid him of the false priest.”¹⁸⁵ By publicly announcing his hatred of Becket Henry II’s words created an attitude of hatred in others that influenced their behavior to harm. Though Henry II did not order his knights to kill Becket and as May notes may not have even intended his knights to kill Becket, he still causally contributed to Becket’s death. The idea being that the knights would not have killed Becket had Henry II not publicly expressed an attitude of hatred, which in turn created a climate in which harm was more likely.

May offers another hypothetical example of two groups, group A and group B. Several members of group A speak out negatively against group B with full knowledge that their public statements may cause violence against group B’s members. While one person of group A who speaks out may not directly cause a violent act to be taken against

¹⁸³ May, *Shared Responsibility*, 46.

¹⁸⁴ May, *Shared Responsibility*, 47.

¹⁸⁵ May, *Shared Responsibility*, 47.

a member of group B, as in the Becket and Henry II case, the person may still be responsible for contributing to a climate that made violence against members of group B more likely.¹⁸⁶

The second way agents who hold racist attitudes but do not harm directly participate in racial harms in society is “by becoming, like the reckless observer..., people who choose to risk harm and yet do nothing to offset this risk.”¹⁸⁷ These are cases where the agent does not publicly express their racist attitudes. May contends that by the agent merely holding the same attitude that is known to cause violence and harm to others, the agent runs the risk of being a harm producer. As mentioned before, May believes that risk takers who may be morally lucky in their actions or attitudes not leading to harm share responsibility for harms caused by others who engage in those same actions and attitudes. In some cases, May contends that by merely holding the racist attitudes, one reinforces or legitimizes the racist attitudes for those who do act out in violence. For example, university faculty members and administration can have a strong impact on students as they are in a position of authority over them. If those faculty members and administrative officials hold racist attitudes, students may feel their own racist attitudes that incite them to violence vindicated.¹⁸⁸

Furthermore, even if those who hold racist attitudes do not have any part in the causal chain that led to violence, they share in the responsibility for the harm. May argues, “insofar as these people do not try to decrease the chances of such violence by changing their own attitudes, given that similar attitudes in others have produced harm,

¹⁸⁶ May, *Shared Responsibility*, 48.

¹⁸⁷ May, *Shared Responsibility*, 46.

¹⁸⁸ May, *Shared Responsibility*, 48-49.

they demonstrate a kind of moral recklessness, similar to that of the reckless observer, which implicates them in the racially motivated violence.”¹⁸⁹ May likens these cases to a sort of Russian roulette scenario. Consider the following hypothetical. Bob tries to kill Fred by aiming the gun at him and pulling the trigger. However, unbeknownst to Bob, the chamber was empty and the gun never went off. Ted takes the same gun, aims it at Fred, and pulls the trigger. This time the gun goes off because there was a bullet in the chamber, and Fred dies. May contends that even though the gun did not go off for Bob, Bob still shares the responsibility for the death of Fred. As May states, “[b]oth people who act recklessly share responsibility not just for the risk but for the actual harm.”¹⁹⁰

Returning to comparative exploitation, when A exploits B by offering B lesser terms, A is behaving in a way that projects the attitude that B is exploitable and is not deserving of equal terms as others, C. That attitude, which I will call the exploitative attitude, can lead to harmful consequences for B, or those like B, in the same two ways that racist attitudes do. First, exploitative attitudes create a climate of harm. That is, when A exploits B, particularly in a public venue, A lets others know that B is exploitable. That, in turn, may lead others to believe B and those like B are exploitable, which may lead to those other individuals exploiting B.

Within the clinical drug trial debate, much of the rhetoric put forth by pharmaceutical companies and researchers is pro-placebo-controlled trials in developing nations even if an alternative medication exists. Dr. Paul S Kelly ran a study in Luksaka, Zambia for the drug nitazoxanide, which treats crypto, an infectious diarrhea, in children.

¹⁸⁹ May, *Shared Responsibility*, 49.

¹⁹⁰ May, *Shared Responsibility*, 9.

Despite alternative drugs, such as albendazole, being available on the market, a PCT was used. Of the 48 children who received placebos, 8 died as a result of crypto.¹⁹¹ Kelly defended the use of placebos, stating,

[t]here is no other way of being absolutely sure that the stuff actually works...It is very very important to do this in third world countries for two reasons. One, because if you misguide people into thinking that your drug works when it doesn't work, you'll be responsible for diverting precious resources away from something else which may also be important. Two, we cannot assume that something which works in other countries will work here...There are geographical differences and we have to be sure that it works where we're planning to use it.¹⁹²

Additionally, a researcher for Schering, who ran a trial for *Shigella* using a PCT,¹⁹³ laments, "I was criticized for doing a *Shigella* trial. They said you are taking advantage! But without the trial, those children would be dead!"¹⁹⁴

Note the rhetoric in those two pieces. They create several black and white dichotomies: either we run the trial as is to make sure the medicine actually works or we run it differently and will never know; that country is different from our country, which means we should run the trial differently or we don't run it at all; and either we run the trial as is and children don't die or children die. These white or black distinctions not only eliminate possibilities of gray areas, but also shift the focus of the actual criticism. The debate is no longer about PCTs versus active control, but rather saving children, as if the only alternative to PCT is no trial. Furthermore, this kind of hyperbolic language masks the actual concern about PCTs and encourages others to engage in similar

¹⁹¹ Shah, *The Body Hunters*, 28-29.

¹⁹² Paul S. Kelly quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006) 32-33.

¹⁹³ *Shigella* is a diarrhea-inducing bacterium that kills a million people yearly worldwide.

¹⁹⁴ Researcher quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006) 36.

behavior. That is evident with the growing number of trials run overseas. From 2001 to 2003, the number of investigators hired to run trials in the United States dropped by 11 percent, while overseas investigators increased by 8 percent.¹⁹⁵ Pharmaceutical companies and hired researchers have created a climate that justifies trials run in developing nations without actually addressing the criticisms, which in turn causes more trials to be run with similar standards in developing nations.

The second way those holding exploitative attitudes but do not harm directly participate in racial harms in society is “by becoming, like the reckless observer..., people who choose to risk harm and yet do nothing to offset this risk.”¹⁹⁶ Recall the example of Bob failing to kill Fred with a gun that Ted then uses to kill Fred. A similar analogy can be made for comparative exploitation and even exploitation more generally. Assume A exploits B with no negative consequences to B. C exploits B in the same manner as A, but this time there are negative consequences for B. Both A and C acted recklessly with regards to B’s welfare, and as a result, according to May, both A and C are responsible for the harmful consequences B suffers. Thus, even if an instance of mutually beneficial exploitation does not harm the exploitee, the exploiter is still morally responsible for any harm that results from that kind of exploitative behavior. For clinical drug trials, that means that even if trial participants in a single trial are not harmed in any meaningful way from a PCT, the pharmaceutical company still bears responsibility for instances when trial participants are harmed.

¹⁹⁵ Shah, *The Body Hunters*, 7.

¹⁹⁶ May, *Shared Responsibility*, 46.

We can imagine scenarios where comparative exploitation leads to incredibly bad consequences, perhaps even death. Because of that, under a traditional counterfactual account, we might say that it is better for B and individuals like B for A not to mutually beneficially exploit B because of the increased likelihood of harm.

Conclusion

In this chapter I crafted ways in which we can understand how not only comparative exploitation, but also cases of mutually beneficial exploitation, may be viewed as harmful. First, we should reject the standard counterfactual comparison theory, which is often used by supporters of PCTs and existing standards in overseas clinical drug trials. Rather, the question of harm depends on the selection of the closest possible world. I argued that the relevant factor for comparative exploitation is choosing the closest possible world where the exploitative interaction is nonexploitative. This differs from the standard counterfactual comparison, which would argue that the closest possible world is one which no interaction took place. For comparative exploitation that means comparing A and B's interaction with A and C's interaction. The difference between the two is what counts as harm to B.

Even if one does not support my framework switch for harm questions, I argued that comparative exploitation is still harmful under the traditional counterfactual comparison account. That is, when A comparatively exploits B, A is promoting an exploitative attitude, one that publicizes B's vulnerability to exploitation. That attitude creates a climate of harm under which B, and individuals like B, are more likely to get exploited, which increases the likelihood that B will get harmed. Furthermore, even if A

does not harm B in their exploitative transaction, the likelihood of severe harm increases.

Thus, under a traditional counterfactual comparison, it is better for A and B to not interact than for A to mutually beneficially exploit B.

Chapter 4: Standard of Care

Introduction

In the previous two chapters, I have argued that trial participants from developing and developed nations ought to be treated similarly. The most common argument against equal treatment is the standard of care argument, which justifies the violation clinical equipoise in international trials. That is, the restraints for the trial, specifically the control group, be set by the usual “standard of care” of the host country. In this chapter, I will challenge that argument. First, I will explore the definitions of “standard of care” and lay out some of the arguments for different standards of care. This section will also identify international and FDA guidelines that discuss the standard of care used in clinical trials. Next, I will generally dispute the argument supporting different standards of care and identify its weaknesses. Then, Ruth Macklin identifies three faulty assumptions proponents of standard of care hold. I will address each one in turn. The second section addresses the use of placebo control trials (PCTs) as the gold standard assumption. I will argue that active control trials (ACTs) provide a reliable alternative, particularly when there is an ethical dilemma, to PCTs. The third section addresses the assumption that the only relevant research question is whether the experimental drug is better than the ‘nothing’ now available in the host country. Not only will I contend that the experimental drug is not better than the ‘nothing,’ but that another relevant research question concerns the risk-to-benefit ratio for trial participants as mandated by international and FDA guidelines. The final section addresses the assumption that the only way of attaining affordable drugs is by testing cheap alternatives. I will contend that

pharmaceutical companies are not fulfilling their burden of making the drug available to the tested population, and that it is conceivable for those companies to sell the drug at a cheap price. In each section I will begin by explaining what the international and U.S. domestic guidelines mandate on that topic. I will specifically look at the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS), and the Food and Drug Administration (FDA)

Standard of Care

The concept of “standard of care” lacks formal definition and has several meanings depending on the context. According to Nicole M. Deming, a mental health professional, the phrase “standard of care” refers to “those practices, procedures, and quality of treatments that a patient should be accorded and a health care provider is obligated to make available.”¹⁹⁷ It may also refer to “the evaluation of a provider’s actions compared to what should have been done in a given situation.”¹⁹⁸ Because medicine is constantly evolving with our knowledge increasing, the current standard of care must also change and evolve. While clearly defined guidelines do exist in some fields, they can easily be outdated if they reference a specific practice rather than a general principle. Though it may be difficult to clearly define standard of care given the dynamic medical climate, Deming argues that we ought to view the standard of care as “a

¹⁹⁷ Nicole M. Deming, "Standard of Care," In *Mental Health Practitioner's Guide to HIV/AIDS* (Springer New York, 2013): 389, accessed April 18, 2013, http://link.springer.com.ezproxy1.lib.asu.edu/chapter/10.1007/978-1-4614-5283-6_82#page-1,

¹⁹⁸ Deming, “Standard of Care,” 389.

level of care below which providers cannot go rather than an aspirational ceiling or level of care to reach.”¹⁹⁹

Within the legal context of malpractice, a doctor’s negligence is determined in relation to the standard of care in that specialty. As Ralph Peeples, Catherine T. Harris, and Thomas B. Metzloff describe,

[i]n medical malpractice cases, the liability of a defendant-physician is a function of negligence and causation. If the defendant-physician has been negligent, and if the proximate cause can be established, then the defendant-physician will be held liable for the plaintiff-patient's injuries. “Negligence,” in turn, is a function of standard of care; failure by a defendant-physician to meet the relevant standard of care constitutes negligence. The standard of care expected of physicians is usually described in terms of “custom”: what is the accepted practice among other physicians practicing in the same specialty?²⁰⁰

The National Institute of Health developed the following expanded concept of standard of care for international research:

- Provision of the same access to research, expenditure on the total care of each subject, and therapeutic drugs shown to be most effective in other locations
- Provision of the same “hotel” facilities, access to technology, general medical care, and other external influencing factors during the trial that were associated with and contributed to the “best proven” use of the drugs elsewhere
- Provision of the same follow up facilities for subjects after completion of the study and the same access to ongoing care
- Research undertaken by a team of the same culture and language group as the subjects, so that the same degree of effective communication, trust, and genuine informed consent is achieved through a legitimate informed decision making process
- Care provided by a research team with equivalent qualifications, training, and expertise²⁰¹

¹⁹⁹ Deming, “Standard of Care,” 389.

²⁰⁰ Ralph, Peeples, Catherine Harris, and Thomas Metzloff, “The process of managing medical malpractice cases: The role of standard of care,” *Wake Forest Law Review* 37 (2002): 878.

²⁰¹ Solomon R. Benatar, and Peter A. Singer, “A new look at international research ethics.” *BMJ: British Medical Journal* 321, no. 7264 (2000): 824.

The ambiguity in all three of these explanations of standard of care, which is at the center of the standard of care debate for international research, is determining the meaning and intent of the “best proven” treatment available. Defending the differing clinical standards, pharmaceutical companies and researchers argue that the standard of care for trial participants be determined by the host nation. Researchers and bioethicists, who are supported the use of a placebo in the AZT trials, maintain that they need only provide the “highest standard of care practically attainable in the host country.... There is no obligation to provide study participants with the highest standard of care attainable elsewhere in the world.”²⁰² In 2000, UNAIDS released a guidance document agreeing with that position.²⁰³

Franklin G. Miller and Howard Brody argue that there is a difference between clinical trials and clinical medicine;

[p]hysicians in clinical practice have a duty to promote the best interests of patients by offering optimal medical care. In [randomized controlled trials], however, physician-investigators are not offering personalized medical therapy for individual patients. Rather, they seek to answer clinically relevant scientific questions by conducting experiments that test safety and efficacy of treatments in *groups* of patients.²⁰⁴

Because of that difference, Miller and Brody maintain that the ethics ought to be different for clinical medicine and clinical trials. Specifically, in clinical trials, investigators do not have an obligation to provide optimal medical care, but rather they

²⁰² Catherine M. Wilfert and James W. Curran, "Science, ethics, and future of research into maternal-infant transmission of HIV-1," *The Lancet* 353, no. 9167 (1999): 1880, quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006), 95.

²⁰³ Shah, *The Body Hunters*, 95.

²⁰⁴ Franklin G. Miller and Howard Brody, "What makes placebo-controlled trials unethical?," 263.

have the obligation to not exploit research participants. To avoid exploitation, investigators need only to ensure that the research participants are not being exposed to excessive risk and that they understand that they are volunteering to participate in an experiment rather than receiving personalized medical care.²⁰⁵²⁰⁶

Industry scientists maintain that the obligation to provide the most optimal treatment to be too onerous. Merck's Laurence Hirsch and Harry Guess make the following arguments against that obligation

[f]irst, none of the methods used in the study may be found to be suitable. . . . Secondly, a single study can rarely identify "best" treatment. . . . Thirdly, a new drug or device may not be approved until several years after the end of a trial. Consequently, providing as yet unapproved treatment to trial participants on completion of the study may conflict with local regulations. Finally, an offer to provide treatment that is otherwise unavailable on completion of the trial might be considered an undue inducement to potential participants.²⁰⁷

That sentiment is supported by a 2001 paper issued by the Pharmaceutical Research and Manufacturers of America;

[i]t is unrealistic and misleading to suggest that [drugmakers] can ensure access to drugs for an given populations. . . . Only local governments, not pharmaceutical companies, can make decisions about initial, and particularly ongoing, access to new drugs. . . . There is a need first to establish an appropriate infrastructure (e.g. roads, transportation, electricity, and water supplies).²⁰⁸

²⁰⁵ Franklin G Miller and Howard Brody, "What makes placebo-controlled trials unethical?", 263.

²⁰⁶ In the previous two chapters, I have argued why preventing optimal medical care in the developing world constitutes exploitation. In this chapter, I will further address why the use of placebos when other treatment exists is unfair and exposes the patients to unnecessary risks.

²⁰⁷ Laurence J. Hirsch and Harry A. Guess, "Some clauses will hinder development of new drugs and vaccines," *BMJ: British Medical Journal* 323, no. 7326 (2001): 1422-1423, quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006), 138.

²⁰⁸ Pharmaceutical Research and Manufacturers Association discussion paper, June 2001, cite din World Medical Association, "Documentation for the Preparation of Note of Clarification on paragraph 30 of the Revised Declaration of Helsinki," September 2003

Admittedly there are practical challenges to providing the best-proven therapies. Some developing countries do not have access to intensive care units, clean needles and equipment to provide some medications intravenously, etc. However, if pharmaceutical companies are willing to spend the money on appropriate infrastructure such as roads and transportation, as will be discussed later in this chapter, should they not also provide the necessary medical equipment for the best proven medical, especially when lives are at stake? In many of the cases talked about throughout this dissertation, such as the Surfaxin case, the best-proven treatment does not involve providing expensive equipment, but rather providing a medication. Moreover, as will be discussed on in the second to last section of this chapter concerning providing cheaper drugs, pharmaceutical companies have the financial means to provide medical treatments and research but choose not to in the interest of profit.

Additionally, proponents of differing standards of care, from now on referred to as the standard of care position, maintain that several key health documents justify it. First, the 2008 revision of the Declaration of Helsinki, the most up-to-date version, states,

[t]he benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be

quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006), 138.

subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.²⁰⁹

Individuals such as Robert Levine interpret “best current proven intervention” to mean what would have otherwise been available to the subjects in their locale.²¹⁰ For example, in the proposed Surfaxin trial, existing market medications were not available on the medical markets of Mexico, Ecuador, Bolivia, and Peru. Since participants would not have access to those medications if they were not enrolled in a trial, the standard of care for those participants would be zero treatment. Thus, the trial would not be doing anything worse than what the participants would have experienced if they did not enroll in the trial.

Second, proponents of standard of care point out that in the guidelines to avoid exploitation in developing nations as developed by Council for International Organizations of Medical Sciences (CIOMS), there is no mention of testing a new drug against existing medications that are available in the developed world but not the host country. Specifically, proponents point out Guideline 10: Research in populations and communities with limited resources, which states,

[b]efore undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated will be made reasonably available for the benefit of that population or community.²¹¹

²⁰⁹ World Medical Association, *Declaration of Helsinki*, World Medical Association, October. 2008, paragraph 32, accessed April 18, 2013, <http://www.wma.net/en/30publications/10policies/b3/>.

²¹⁰ Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 224.

²¹¹ “International Ethical Guidelines for Biomedical Research Involving Human Subjects.”

The guideline seeks to avoid exploitation in research by ensuring that the research not only serves to help in the health needs the tested population, but also to ensure lasting beneficial effects through the sharing of knowledge. This latter stipulation, as discussed in the introduction, is often ignored by pharmaceutical companies. Drugs are not made readily available at an affordable rate for the tested populations. This topic will be discussed in further detail later in this chapter.

Note, also, that the guideline makes no mention of trial procedures. That is, the guidelines do not include a requirement that the trial's procedural standards be the same as those run in developed nations. Ruth Macklin also recognizes that gap in the guideline, and sees it as a gateway for abuse by researchers. To bolster that point, Macklin refers to a commentator on the guideline who, while embracing the general aim against exploitation in research, uses an example that is open to precisely the opposite charge. The commentator states,

[t]he purpose of this guideline seems to be to prevent exploitation of poor communities for research purposes when the research is unlikely to benefit them. This aim should be supported but at the same time research in developing countries should not be inhibited but encouraged as a means of developing greater international collaboration. The test is whether in the country or territory concerned research subjects would be deprived of an effective intervention solely on account of the proposed research. If so it would be unethical but not otherwise. For example, a randomised trial of an inexpensive and simple method of cervical screening (e.g. a blood test) could be compared with no screening in parts of India where there was no screening at all.²¹²

Despite agreeing with CIOMS's general condemning of exploitation in developing nations, this commentator, like some others, are missing an obvious avenue of

²¹² Anonymous quoted in Ruth Macklin, *Double Standards in Medical Research in Developing Countries* (Cambridge: Cambridge University Press, 2004), 110.

exploitation - testing against no treatment when a viable one exists in a developed nation.

As Macklin rightly argues

[n]one of the women in this study in India would receive the best current method of screening for cervical cancer, some would receive the experimental screening method, and others would not be screened at all. An ethically superior research design would compare the proposed inexpensive method with the best current method - the pap smear - to determine whether the proposed new method is as good as, or almost as good as, the best diagnostic method.²¹³

In sum, CIOMS Guideline 10, while providing some necessary regulations, does not offer a sufficiently full account of what an ethically sound clinical trial requires to prevent exploitation. By not directly addressing trial procedures, specifically the use of PCTs and defining “best current method,” researchers and pharmaceutical companies use the loophole to their advantage and argue that their PCTs trials are ethical

There are many reasons to reject the standard of care argument. While this entire chapter will argue that there should not be differences in care, let us argue against the structure and merits of the argument here. First, it seems wrong to interpret the Declaration of Helsinki to intend the best-proven method in the host country. Had the framers intended to contextualize best proven method, it seems that they would have rewritten that paragraph to say “best proven method in the host country,” or to use the phrase “the standard of care in the host country.” Since there is no context, a more natural interpretation seems to be best proven method, period. That is, the best proven method in existence. This exact debate over interpretation has a long history for the Declaration of Helsinki leading to its many revisions. Its current phrasing is in part a

²¹³ Macklin, *Double Standards in Medical Research in Developing*, 110.

reflection of the ethical controversy over the use of a placebo in the AZT trial.²¹⁴ Despite the World Medical Association's efforts to clarify, the wording remains ambiguous as to intent.

If, however, we are to assume that the Declaration intends the former, the best-proven method in the host country, the declaration becomes more ambiguous. How does one determine what the "standard of care" is in a country? Does that include available pharmaceuticals, commonly used procedures, sanitary conditions, ethical regulation, consent guidelines, etc.? As Macklin argues, the phrase standard of care, "invites confusion because of its ambiguity and the many different interpretations placed upon it by commentators. Despite the widespread use of the phrase 'standard of care' in discussions and debates, there has been little conceptual clarity."²¹⁵ Adding to the confusion, as Macklin points out and as I have suggested in this section, the phrase "standard of care" does not appear in any international declarations or guidelines. With no strict guidelines or regulations, researchers are afforded the ability to interpret standard of care in any manner that they like. A simpler solution is to assume that the Declaration intends best-proven method in existence, which is less ambiguous.

A second reason to reject the standard of care argument is, as Macklin argues, the argument is the lowest-common-denominator basis for determining ethical obligations. That is, providing the same standard of care to trial participants that they would be receiving from their country anyways if the trial were not to take place, seems to be the absolute minimum that researchers could do. Surely, we ought to do more, if for no other

²¹⁴ Macklin, *Double Standards in Medical Research in Developing*, 47.

²¹⁵ Macklin, *Double Standards in Medical Research in Developing*, 39.

reason that out of our adherence to the principle of beneficence. Applying beneficence to research, Macklin and others suggests entails maximizing benefits while minimizing harm to the trial participants.²¹⁶ Surely that demands more of researchers than the bare minimum. Because as Macklin asserts, “[s]ince the research subjects themselves are surely among those who should be counted in seeking to maximize benefits, it follows that providing a higher standard of care during the research, when that is feasible, is ethically preferable to providing the minimal standard dictated by background conditions in the country or region.”²¹⁷

Furthermore, a third reason to against the standard of care argument is that under this framework, the amount of care a patient receives depends upon economic conditions of the host country rather than a normative concept. The standard of care argument is an interpretation of guidelines concerning how trials *ought* to be run and how trial participants *ought* to be treated in order to prevent exploitation. If one wants to frame a normative concept on economic affairs, a normative justification for doing so is needed. However, there is little normative justification for the standard of care arguments offered from its supporters. As Peter Lurie and Sydney M. Wolfe explain, “[i]n developing countries, the standard of care ... is not based on a consideration of alternative treatments or previous clinical data, but is instead an economically determined policy of governments that cannot afford the prices set by drug companies.”²¹⁸ Lurie and Wolfe also reveal a deeper worry: the perpetual cycle of limited care created by the drug

²¹⁶ The risk-to-benefit ratio will be discussed in further detail in a later section of this chapter.

²¹⁷ Macklin, *Double Standards in Medical Research in Developing*, 39.

²¹⁸ Lurie and Wolfe, “Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries,” 856.

companies. That is, as discussed in the introduction and in the next section, it is to drug companies' financial advantage to use PCTS and offer as little care as possible to trial participants. According to the standard of care argument, they need not provide the best alternative treatment because it is not available in the host country. However, the reason host countries do not have access to the best alternative treatment is because drug companies do not sell it to the host countries at an affordable price. Thus by keeping the prices of drugs and treatments high, drug companies are preventing host countries from adopting new treatments as the standard of care for its citizens, which then allows drug companies to save money by not offering it to trial participants when they run a future trial in that host country. Drug companies have created the best possible outcome for themselves. They are justifying their treatment of trial participants through appeal to conditions that the drug companies, themselves, have created.

Not only do drug companies save money by not offering alternative therapies to participants in developing nations, but also the use of a PCT allows them to run the trial more quickly and move the drug through the FDA approval process faster. As Macklin explains, "[i]n addition, the US Food and Drug Administration prefers a placebo-controlled study whenever that design is ethically defensible . . . To industry's advantage, the ability to compare a new drug with placebo shortens the time of the study and makes the data more readily acceptable to the FDA, both of which lead to quicker profits for experimental products that prove to be efficacious."²¹⁹ Thus, it is the pharmaceutical industry's benefit monetarily to argue that PCTs are ethically defensible, hence, the standard of care argument.

²¹⁹ Macklin, *Double Standards in Medical Research in Developing*, 8.

Defenders of the standard of care argument, according to Macklin, are making three flawed assumptions. First, PCTs are the gold standard even in circumstances where using that methodology compromises ethical standards. Second, the only relevant research question responsive to the health needs of the host countries is “Is the experimental product being studied better than the ‘nothing’ now available to the population?” Third, the only way (or best way) of obtaining affordable products is to test cheap alternatives to replace the expensive ones used in developed nations.²²⁰ In the following sections, we will discuss each of the assumptions in turn.

Assumption 1: PCTS as the Gold Standard

Proponents of the standard of care argument, as discussed, contend that in countries where there is no existing therapy, a PCT is ethical as the placebo is not worse off than the treatment participants would be receiving had they not enrolled in the trial. If one does not accept that argument, proponents then make reference to the second bullet point in the Declaration of Helsinki: “[w]here for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.”²²¹ That is, the PCT is needed for scientifically sound methodological reasons, and trial participants are not being subjected to any additional risk due to the trial. If they receive the placebo, they are only enduring the risk they are already facing from the illness if they do not enter the trial.

²²⁰ Macklin, *Double Standards in Medical Research in Developing*, 64-65.

²²¹ *Declaration of Helsinki*, paragraph 32.

In order to understand the need for researchers to set PCTS as the gold standard for optimal trial results, let us look at the regulations and guidelines the FDA sets for control choices. As many drug companies seek FDA approval to market their drug in U.S., the regulations and guidelines put forth by the FDA are often the foundation for procedure choices. Refusing to adopt the 2001 revision the Declaration of Helsinki, the FDA's regulations and guidelines concerning PCTs are even vague and lax.²²²

Regulations concerning preference of control can be found in the Code of Federal Regulations. Title 21 Part 314 Section 126 discusses the choice of ACT over PCT.

(iv) *Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.²²³

At best this regulation is vague. It states that an ACT should be used where the placebo or no treatment would be contrary to the interest of the patient, but does not unpack what they intend by "interest of the patient." Furthermore, the regulation goes on to say that you can also use a placebo control in addition to an active control. The key part of this regulation, however, which is echoed in much of the pro-PCT literature, is the emphasis

²²² Shah, *The Body Hunters*, 135.

²²³ "CFR- Code of Federal Regulations Title 21," U.S. Food and Drug Administration, accessed April 18, 2013, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126&SearchTerm=placebo>.

on effectiveness and demonstrating a difference between the existing therapy and the new therapy.

In their article “When placebo controlled trials are essential and equivalence trials are inadequate,” Martin R Tramér et al. analyze the value of ACTS versus PCTS in ondansetron trials.²²⁴ They found that in many of the ACTS, there was no difference between ondansetron and its active control, but as they argue no difference does not necessarily mean equivalence. As they contend,

[t]he only conclusions that can be drawn if both drugs show similar efficacy are: (a) both drugs are effective to a similar degree; (b) both drugs are equally ineffective; or (c) the trial design was inadequate - for example too small - to show the real difference between the two treatments. In equivalence trials we need to know that both treatments were indeed effective in an A versus B comparison of two active drugs. To meet this criterion we need to know the extent of the placebo response and that it does not vary.²²⁵

In other words, ACTs only allow for a comparative claim: how effective is the new drug as compared to how effective the old drug is. As Tramér et al. argue, there needs to be some evaluation of the new drug on an absolute scale. That is how effective is the drug versus no other drug being given.

In his comparison between PCTS and ACTS, Mario Castro identifies the five most common arguments made by PCT supporters. First, a double blind, randomized PCT is the most rigorous test for treatment efficacy. This is the line of argumentation used by Tramér et al. Second, because a PCT offers the opportunity to compare

²²⁴ Ondansetron is a drug used to prevent nausea and vomiting caused from cancer chemotherapy, radiation therapy, and surgery. “Ondansetron,” MedlinePlus, accessed April 18, 2013. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601209.html>.

²²⁵ Martin R. Tramér, D. John M. Reynolds, R. Andrew Moore, and Henry J. McQuay, “When placebo controlled trials are essential and equivalence trials are inadequate,” *BMJ: British Medical Journal* 317, no. 7162 (1998): 876-877.

outcomes under maximal “treatment separation”, fewer patients are needed than would be required for an ACT. This, in turn, increases the likelihood of detected benefit and/or harmful treatment-related effects. Third, “a placebo group can be used as an ‘add on’ to standard of care in comparison to an investigational treatment added to standard of care.”²²⁶ That allows researchers to evaluate the true benefit or risk of a new therapy. Fourth, a PCT is justified if there is a high rate of placebo response or if the standard treatments are only partially effective. Fifth, PCTs prove essential in determining trial endpoints when typically subjective measures are used due to variation in perception and reporting of patient-reported outcomes.²²⁷

Let us consider each of those arguments in turn. First, I will address the first argument - PCTs are the most rigorous test for treatment efficacy- and the third argument - a PCT allows the placebo group to be used as an ‘add on’ to standard of care versus added to standard of care. Both arguments boast that PCTs are the best at determining the efficacy and benefits of a new therapy. While there is no denying that a placebo control group maximizes the tested treatment’s efficacy as it is being compared to no treatment, there are other important measures that can only be achieved with an active control group.

Though in the cases we are examining where the studies take place in developing nations where no existing treatment exists, the tested drug will be sold in the developed world where alternative treatments do exist. Thus, it would seem preferable to

²²⁶ Mario Castro, "Placebo versus Best-Available-Therapy Control Group in Clinical Trials for Pharmacologic Therapies Which Is Better?," *Proceedings of the American Thoracic Society* 4, no. 7 (2007): 571.

²²⁷ Castro, “Placebo versus Best-Available-Therapy Control Group in Clinical Trials for Pharmacologic Therapies Which Is Better?,” 571.

understand how a new treatment would function in a general population where alternative treatments do exist. ACTs provide that kind of data. As Castro explains, ACTs “work well in late phase II and III trials where the goal is to test a new therapy in the planned manner of use in the general population.”²²⁸

In order to understand Castro’s argument, let us briefly examine the four phases of a clinical trial. In phase I, the drug is tested on a small number of healthy volunteers (between 20 and 80) to determine dosage, identify acute side effects, and document how the drug is metabolized and excreted. In phase II, the drug is tested on a larger set of participants (between 100-300) who have the disease that the drug could potentially treat. The goal of phase II is for researchers to gather safety data, preliminary evidence of the drug’s effectiveness, and to refine research methods for future trials of this drug. If the results of phase II indicate that the drug may be effective and the risks are considered acceptable, the drug moves on to phase III. In phase III, the drug is tested on a larger number of participants with the disease intended to be helped by the drug (between 1,000-3,000). The drug’s effectiveness is further tested, side effects are monitored, and the drug is sometimes compared to a standard treatment if one is already available. Since this phase involves more individuals being tested over longer periods of time the less common side effects are more likely to surface. Finally, in phase IV, the drug is

²²⁸ Castro, “Placebo versus Best-Available-Therapy Control Group in Clinical Trials for Pharmacologic Therapies Which Is Better?,” 572.

approved and on the market, and trials are conducted to determine the long-term benefits and risks of the drug.²²⁹

Returning to Castro's argument, since phase II and phase III focus on the drug's effectiveness and identifying risks and side effects, it makes sense to make the conditions of the trial such that they mirror the actual kinds of populations where the drug is intended to be used. In most cases, that is in developed nations, where alternative treatments exist. Furthermore, by comparing existing treatments with the new treatment, researchers will be better able to identify unique side effects of the tested treatment. For example, perhaps all medications of a certain type cause dry mouth, but the new experimental drug has higher incidences of headaches. Comparison amongst treatments is necessary in order to determine if the new medication is an improvement in terms of minimizing side effects. Overall, it seems that to best understand how effective a drug will be in developed nation populations, that ACTs be used. Castro fine tunes this point, [t]he use of best-available-therapy control groups also provides pivotal evidence of efficacy and provides further information with regard to potential side effects from that medication. This allows one to weigh the balance between efficacy versus side effects between two different therapies."²³⁰

The second argument is that PCTs require fewer patients, which in turn subjects fewer patients to potential harmful effects of treatment. The strength of this argument relies on the assumption that the tested treatment is potentially more harmful than no

²²⁹ "Inside Clinical Trials: Testing Medical Products in People," U.S. Food and Drug Administration, updated April 12, 2013, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm>.

²³⁰ Castro, "Placebo versus Best-Available-Therapy Control Group in Clinical Trials for Pharmacologic Therapies Which Is Better?," 572.

treatment at all. In many of the trials under question for ethical violations, the treatment being tested is not an entirely new drug where researchers have no idea of the potential harmful consequences. In the AZT trial, a lower dose of the existing treatment was being tested, and in the surfaxin trial, a new surfactant drug was being tested when many others already existed on the market. In those trials, the harm posed to the those individuals receiving the new medications is by far outweighed by the harm undergone by those receiving no treatment in the placebo control group, where harm and potential death of aids and respiratory distress syndrome is guaranteed.

Additionally, while PCTs may require fewer patients, the dropout rate is much higher for PCTs as compared to ACTs. In a study performed to compare dropout rates for PCTS and ACTS for antipsychotic drugs, George Kemmler, et al. reviewed 31 trials - 11 PCTS and 20 ACTS. They found the dropout rates to be notably higher for PCTS than ACTs. For all antipsychotics trials (classical and second-generation), PCTS had a mean dropout rate of 48.9% while ACTS had a mean dropout rate of 30.3%.²³¹

Kemmler et al suggest that one reason for the higher PCT dropout is that patients' willingness to participate is negatively affected upon finding out that the control will be receiving a placebo.²³² Regardless of the cause, empirically PCTS have higher dropout rates than ACTs, which has two implications: either more patients have to be involved in the PCT to maintain enrolled numbers, or the dropout is so high that an additional trial is

²³¹ Georg Kemmler, Martina Hummer, Christian Widschwendter, and W. Wolfgang Fleischhacker, "Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis," *Archives of general psychiatry* 62, no. 12 (2005): 1306-1308.

²³² Kemmler, Hummer, Widschwendter, and Fleischhacker, "Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis," 1310.

needed to prove efficacy. Either way, more participants are needed which means more participants are being subjected to potential harmful treatment-related effects.

The fourth argument is a PCT is justified if there is a high rate of placebo response or if the standard treatments are only partially effective. The first part of this argument-high rate of placebo response- was addressed under the first and third arguments concerning the testing of efficacy. The latter part of that argument - standard treatments are only partially effective - is unclear. First, what constitutes a standard treatment being only partially effective? If it improves the quality of life of the patients, some treatment is preferable to no treatment. So long as there is health benefit to be had, there seems no reason to treat partially effective standard treatments any differently than wholly effective standard treatments. Moreover, if what is at issue is the efficacy of the tested treatment, assuming the tested treatment is significantly more effective than the standard treatment, then ACTs would seem to show that statistical difference. That is, the margin of effectiveness of the tested treatment would be of statistical significance over the standard treatment. Finally, those cases that cause the most ethical concern do not have partially effective treatment, but rather wholly effective treatments. Thus, this argument has little weight in our current discussion.

The fifth argument is PCTs prove essential in determining trial endpoints when typically subjective measures are used due to variation in perception and reporting of patient-reported outcomes. Trial endpoints are a “measurable outcome that indicates an intervention’s effectiveness.”²³³ Since using a placebo control compares the

²³³ Cecily Jenkins, “How to Interpret Scientific Research and Clinical Trial Results,” *Alzheimer’s Disease Information Network Monthly E-Newsletter* 10 (2009), accessed

experimental drug to no treatment, the effectiveness is more easily noticeable, as any change in those taking the experimental drug is either a direct benefit or side effect of the drug. As just discussed, there are more factors and questions surrounding a drug's efficacy. However, I am willing to grant that PCTs may be more helpful in determining trial endpoints. Despite this concession, this argument is not enough to solidify the use of PCTs versus ACTs particularly when clinical equipoise is violated. That is, there is guaranteed harm from disease for patients who are in the placebo control.

As a final note on the topic of PCTs versus ACTs, research shows that physicians show a preference for ACTs over PCTs. In a study completed by Scott D. Halpern, MSCE, et al. in 2002, physicians were asked whether they would refer their hypertensive patients to a PCT or an ACT study for a new hypertensive drug. Of the 651 physicians who completed the questionnaire, 67.1% indicated that they would probably or definitely encourage their hypertensive patients to enroll in an ACT. Only 29.7% would encourage enrollment in the PCT. Physicians with prior research participation were more likely than those without to encourage enrollment in ACTs.²³⁴ To explain these results, Halpern et al. report

[p]hysicians viewed the ACT as providing more useful information for their personal practices, as contributing more broadly to a public health benefit, as offering enrolled patients a greater chance for personal benefit and as being less likely to place subjects at unnecessary risks... In open-ended responses, physicians generally offered 2 reasons for preferring ACTs. Some felt that 'if the patient has hypertension and is responding to medication, it's unethical to put him in a

April 18, 2013, http://www.adcs.org/research/eNewsLetter/ADIN%20E-Newsletter_August_2009.pdf.

²³⁴ Scott D. Halpern, Peter A. Ubel, Jesse A. Berlin, Raymond R. Townsend, and David A. Asch, "Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs," *Journal of general internal medicine* 17, no. 9 (2002): 691.

placebo trial.’ Others focused on the value of the information provided by the different trial designs. As one said, ‘I am interested in [the] benefit of newer medications versus old. We have already established that antihypertensives are better than placebo.’²³⁵

Furthermore, when asked which of ACT or PCT is more justifiable as a means of testing new antihypertensive drugs, 67.3% of physicians responded that ACTS were more justifiable than ACTS; whereas, only 10.4% thought PCTS were more justifiable.²³⁶

In this section, I challenged the notion that only PCTs can provide the adequate data necessary in testing an experimental drug. I have also demonstrated that a preference for ACTs over PCTs exists in both the minds of participants and physicians who recommend trials to their patients. I want to propose one more challenge for PCT supporters. If PCTs are truly the gold standard, producing the best results for medical research, then why are they not run in developed nations? Recall that in chapter 1, I describe how pharmaceutical companies run PCTs in developing nations because it would be unethical to run them in developed nations as the standard of care in developed nations has existing alternative treatments. That is, if the trial were to be run in the developed nation, it would necessarily have to be an ACT. Rather than challenge that ethical constraint, clinical trials have been exported to developing nations. One would think that if PCTs would as medically and statistically necessary as proponents argue, then there would be a strong push to allow PCTs in developed nations, but there is not.

²³⁵ Halpern et al., “Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs,” 691.

²³⁶ Halpern et al., “Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs,” 691.

Assumption 2: The only relevant research question responsive to the health needs of the host countries is “Is the experimental product being studied better than the ‘nothing’ now available to the population?”

I interpret this assumption as asking the question whether the only relevant research question responsive to the health needs of the host countries is “Is the experimental product being studied better than the ‘nothing’ now available to the population?” My answer is no. There are other relevant questions and considerations that ought to factor into the equation of whether the researchers are being responsive to the participants’ health needs. Specifically, in this section, I will argue that guideline precedent calls on researchers to examine the risks and benefits to the research participants, and if we do so, then we find that for developing nation participants, the risks exceed the benefits.

The comparison of risks undergone by participants and the benefits received by the participants and other communities is mentioned many times in the various guidelines governing clinical research. The Declaration of Helsinki states,

[e]very medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens in the individuals and communities involved in the research in comparison with the foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.²³⁷

The Declaration goes on to explain,

[p]hysicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study

²³⁷ *Declaration of Helsinki*, paragraph 18.

when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.²³⁸

CIOMS identifies three general ethical principles that all research involving human subjects ought to be conducted in accordance with: respect for persons, beneficence, and justice. The latter two specifically discuss risks and benefits to participants. In regards to beneficence,

[b]eneficence refers to the ethical obligation to maximize benefits and to minimize harms. This principle gives rise to norms requiring that the risks of research be reasonable in light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects.²³⁹

Under the principle of justice, the Council argues that concerning human subject research, the principle primarily refers to distributive justice, “which requires the equitable distribution of both the burdens and the benefits of participation in research.”²⁴⁰

Guideline 8 under CIOMS’ International Ethical Guidelines for Biomedical

Research Involving Human Subjects goes on to address the risk-to-benefit ratio directly;

[f]or all biomedical research involving human subjects, the investigator must ensure that potential benefits and risk are reasonably balanced and risks are minimized.

- Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject, in the light of foreseeable risks and benefits, as any available alternative. Risks of such ‘beneficial’ interventions or procedures must be justified in relation to expected benefits to the individual subject.
- Risks of interventions that do not hold out the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be

²³⁸ *Declaration of Helsinki*, paragraph 20.

²³⁹ “International Ethical Guidelines for Biomedical Research Involving Human Subjects.”

²⁴⁰ “International Ethical Guidelines for Biomedical Research Involving Human Subjects.”

justified in relation to the expected benefits to society (generalizable knowledge). The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.²⁴¹

Note that if benefits for the individual are not realizable, then there must be proven benefit to society as in generalizable knowledge. As we have discussed in the introduction and will discuss in the next subsection, that generalizable knowledge is only made available to the developed world.

The FDA addresses the balance between risk and benefit in its criteria for Institutional Review Boards (IRB) approval of research;

[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that should would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy as among those research risks that fall within the purview of its responsibility.²⁴²

Though vague in detail, the common go-to human research guidelines all offer rhetoric of maximizing the benefits and minimizing the risk for the human participants - a favorable risk-benefit ratio.

In an effort to clarify what is intended by a favorable risk-benefit ratio Ezekiel J Emanuel, David Wendler, and Christine Grady offer explanations of the ratio. They argue,

[c]linical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to

²⁴¹ “International Ethical Guidelines for Biomedical Research Involving Human Subjects.”

²⁴² “CFR- Code of Federal Regulations Title 21.”

individual subjects are enhanced, and the potential benefits to the individual subjects and society are proportionate to the or outweigh the risks.²⁴³

The last condition of proportionality continues to be a vague area and a center for debate in the literature. In general terms, Emanuel et al. intend,

the more likely and/or severe the potential risks the greater in likelihood and/or magnitude the prospective benefits must be, conversely, research entailing potential risks that are less likely and/or of lower severity can have more uncertain and/or circumscribed potential benefits²⁴⁴

Admittedly, some risks and benefits are unquantifiable, and a more precise standard of evaluation is needed, particularly for cases that are not clear-cut. However, I do not believe the case of PCTs in developing nations to be a vague case.

In analyzing the risk-benefit ratio for clinical drug trials in developing nations (particularly PCTs), let us first look to the risks undergone by participants. In any clinical drug trial, be it ACT or PCT, participants undergo risk, - risk of complications from experimental procedures and risk of potential side effects from the experimental drug. For example, in 1996 Pfizer used a Nigerian meningitis epidemic in children to test a new drug. Of those who received the experimental drug, eleven died, and 200 others became deaf, blind, or lame.²⁴⁵

The risk to participants increases when pharmaceutical companies and researchers cut corners in an effort to save money and cut down trial time, as often happens in developing nations. In that same Pfizer study, the experimental drug was given to children orally. In the United States, any treatment of meningitis is normally given intravenously - a faster-acting route of administration. The oral form of the drug had

²⁴³ Emanuel, Wendler, and Grady, "What makes clinical research ethical?," 2705.

²⁴⁴ Emanuel, Wendler, and Grady, "What makes clinical research ethical?," 2705.

²⁴⁵ Macklin, *Double Standards in Medical Research in Developing*, 99.

never been tested previous to the trial in Nigeria. Pfizer took additional short cuts in the Nigerian trial. While industry guidelines mandate that all children in the trial must be given a spinal tap a day or so after administering the drug to see if it's working, Pfizer made the spinal tap optional. Moreover, children were initially supposed to have blood tests run on two separate occasions; however, the requirement of the second blood test was abandoned due to staff shortage.²⁴⁶

One might argue in epidemic situations, where the risks are already high for patients, people are willing to take higher risks for a cure than they would have been otherwise. While that argument may justify the patients' consent to lower standards, as they have no other treatment options, it does not, however, justify Pfizer's lowering of standards. Patients' willingness to accept inferior treatment does not diminish Pfizer's obligation to provide adequate care. As will be discussed at the end of this chapter, consent does not justify inferior treatment.

There are more examples of researcher's cutting corners in developing nations. In 1997 Jay Brooks Jackson ran a trial in Uganda testing the effectiveness of nevirapine - a drug to be used in preventing mother-to-child transmission of HIV. Since the trial was not designed to for FDA approval, but rather as a public health inquiry, several corners and FDA guidelines were cut, which exposed trial participants to risk as well as future patients. For example, the drug was supposed to remain at room temperature. Jackson claims that it was, but the temperature wasn't monitored. Additionally, researchers did not report adverse events as serious if it was managed without hospitalization, even though FDA rules would categorize those events as serious. Jackson argued that though

²⁴⁶ Macklin, *Double Standards in Medical Research in Developing*, 100.

FDA's requirement for documentation is understandable, as the FDA has seen a lot of scams, the hospital in Uganda, Mulago Hospital, does not keep records. Moreover, there was no one available in Uganda to monitor the research to ensure conformity with FDA guidelines.²⁴⁷ While Jackson's plight sheds light on practical problems of guideline enforcement, it does not, however, justify the cutting of corners.

India has, also, had several incidents of guideline violations. In 2001, a researcher from Johns Hopkins tested an experimental cancer drug on dozens of cancer patients, which had not even been proven safe in animals. In 2003, an Indian pharmaceutical company sponsored clinicians who administered an experimental drug, letrozole, to over four hundred women, who were told that the drug boosts fertility. However, according to the FDA, letrozole is an anticancer agent which is toxic to embryos, and moreover, letrozole has yet to be approved for medical use.²⁴⁸ These violations not only put participants at a higher risk level than is outlined in international guidelines, but at a higher risk level than participants would have been had the trial been run in a developed nation where there is a greater level of ethical enforcement.

In addition to the increased risk from cutting corners, participants are put at higher risk with the use of a PCT versus an ACT. Many argue that there is little risk to the placebo control in developing nations, as they would be receiving no care had they not enrolled in the trial. Recall that in the last chapter, I argue that this is the wrong comparison to be made. Rather than comparing the developing nation participant's actual world with one in which he did not enroll in the trial, we ought to compare the

²⁴⁷ Shah, *The Body Hunters*, 109-110.

²⁴⁸ Shah, *The Body Hunters*, 113.

participant's actual world with the world in which they lived in a developed nation.

Because as described in the introduction, many of the PCTs in developing nations would be run as ACTs in developed nations, we ought to compare the risk of using a PCT over an ACT.

Assuming that the cutting corners risks just described would be the same for a PCT versus an ACT, the primary risk for a PCT over an ACT is for the control group that is receiving the placebo. Let us look at some of the harm endured by the placebo group in specific cases. In March 1999, the Center for Disease Control and Prevention (CDC) announced results of their PCTs of AZT run in Côte d'Ivoire and Thailand. They wanted to compare the HIV transmission rate when a mother is given a few weeks of AZT versus a placebo. The short course of AZT halved the transmission rates, and of the over three hundred women receiving the placebo, nearly seventy of their babies were born HIV-positive.²⁴⁹ This case is particularly troubling for a couple of reasons. First, as seen with many other drugs, one of the major reasons why we are testing AZT at shorter courses is because the host countries, which are most in need of AZT, cannot afford the medication. For those infants who were born HIV-positive despite their mothers' receiving the short course, roughly half of the tested group, their HIV status is in part the result of pharmaceutical companies keep the prices too high for AZT. As a result of pricing, rather than running trials for new medications, the CDC must run trials to see if AZT can be used at lower doses to reduce costs. A much easier solution would be for pharmaceutical companies to lower prices so such trials would not have to be run.

²⁴⁹ Shah, *The Body Hunters*, 88 and 95.

Second, the CDC unnecessarily ran a PCT when there was an option of an ACT. Those fetuses in the placebo group had no improved chance of not being born HIV-negative. A commonly described scenario analogous to this one is the woman who walks by a baby drowning in a puddle of water. Should not the woman turn the baby over when it would cost the woman so little and benefit the baby so greatly. Instead of a puddle of water in the AZT case, the babies are in a puddle of HIV.

Third, perhaps most disturbing is that the CDC would not have been able to run the trial in the United States or any other developed country where AZT is available on the market because it would have been unethical. As Macklin describes,

[o]nce it had been shown to be effective in reducing the transmission of HIV from mother to child, the expensive AZT treatment became the standard therapy for HIV-positive pregnant women in the US and other industrialized countries. It would surely be unethical to withhold from women in a research study an effective treatment they could obtain as part of their routine medical care. But since women in the developing countries did not have access to any treatment whatsoever, they would not be made worse off by participating in the study than they would otherwise have been.²⁵⁰

In other words, the woman does not have to turn over the baby drowning in the puddle because the baby would have died anyways had she not come along.

These arguments apply to the following situations as well. In the early 2000s, gastroenterologist Paul S. Kelly, hired by Romark, in collaboration with the University Teaching Hospital ran a trial in Zambia for nitazoxanide, a drug to treat crypto, diarrhea, in both children who were HIV-negative and children who were HIV-positive. Even though alternative drugs such as albendazole existed, a placebo control was used. Twenty-five of the HIV-negative children with crypto were given a three-day course of

²⁵⁰ Macklin, *Double Standards in Medical Research in Developing*, 15.

the experimental drug, all of which improved. Twenty-two HIV-negative children with crypto were in the placebo group. Four of them died a week later. For the HIV-positive children with crypto, twenty-five were given a three-day course of nitazoxanide, even though evidence suggested that such a short course would not work. Five children died. Twenty-four of the HIV-positive children were in the placebo control, and four died.

Sonia Shah describes the heightened risk these children underwent because of the placebo control,

[i]t would be useful to know how the surviving children and the relatives of the dead felt about the experiment after it was all over. Did they know, as their doctors must have, about the evidence that better cures for their children could have been had with antiretroviral therapy, lengthy treatment with nitazoxanide, or alternative drugs, such as albendazole? Was the history of the drug and the experiment - the facts that patients in the United States had refused to be involved in an experiment such as this, and that it was designed to launch a drug aimed at societies far distant from their own - made clear to them? These are unknowns. Their experiences, save perhaps for a few lines of technical data, went unrecorded. Like so many experimental subjects in poor countries, they melted back into a social sphere that science rarely penetrates.²⁵¹

In the proposed Surfaxin trial, half of the 650 participating babies would be assigned to a placebo group when four other known treatments exist on developed nations' markets. That is putting 325 babies with respiratory distress syndrome in serious danger of dying when they are in an environment that could provide them the care they need. There are many more cases of developing nation trial participants in the placebo control group succumbing to their illnesses. While it may seem there is no additional risk as that would have been their fate had the trial not taken place, that position assumes the wrong counterfactual question. If we compare the risk of a developing nation participant

²⁵¹ Shah, *The Body Hunters*, 29.

with the risk of a developed nation participant, we can see that the developing nation participant has the additional risk of being place in a placebo-controlled trial.

Let us now look at the benefits trial participants receive. Just as in clinical trials in the developed world, developing world participants that are not in the control group receive the experimental medication that may aid in combatting their illness. Both participants in the control group and experimental groups receive over all general medical care. For example in SmithKline Beecham's Havrix trial, a hepatitis A vaccine was tested on 40,000 children in Thailand. All of the children in the trial would receive a hepatitis B vaccine and a hepatitis A vaccine if it proved effective. Additional medical services were augmented; "[t]he research team contracted with community public health workers to examine all enrolled children absent from school at their homes, to provide necessary care, and, if appropriate to arrange transfer to the district or provincial hospital."²⁵²

Moreover, there were benefits for the populations. New refrigerators were provided to public health stations that did not have adequate refrigeration to store vaccines medicines and blood specimens. Those public health stations that lacked FM wireless network access linking them to provincial hospital consultants were given access. When the source of the hepatitis A's rapid spreading was linked to deficiencies in toilet facilities, hand-washing facilities, and water storage, the researchers contracted to have the improvements implemented. Public health workers were provided with an unlimited supply of disposable syringes and needles and were given training on how to reduce the incidence of blood-borne diseases. All interested government personnel

²⁵² Hawkins and Emanuel, "Two Case Studies: Havrix, Surfaxin," 56.

working on the trial, including 2,500 teachers, public health workers, nurses, technicians and physicians, were given the hepatitis B vaccine. In the process of tracking the deaths of all enrolled participants, researchers identified motor vehicle accidents as a major cause of mortality in the region and recommended corrective measures. Finally, the training and experience the Thai researchers garnered through the Havrix trial may have facilitated subsequent trials.²⁵³

While it may seem that the SmithKline Beecham went above and beyond to help the participating children and the Thai community, it should be noted that, the same measures would be taken if the trial were to be run in the developed world. The difference is that much of the infrastructure- including wireless networks, access to disposable syringes and needles, and the population receiving the hepatitis B vaccine - already exist in the developing world so there is no need for SmithKline Beecham to provide it. This is true of clinical drug trials run abroad in general. The health care in developing nations is so poor that any additional medical care offered would be considered part of appropriate medical care in the developed world. If we view these benefits through my counterfactual lens, described in the previous chapter, then the developing world participants are not receiving any additional benefit than the developed world participants would have received had the trial been conducted there.

It is important to note which benefits developing nation participants are not receiving that developed nations participants are receiving, specifically technology and research garnered from the study and the availability of the tested drug should be proven effective at an affordable rate. The next subsection of this chapter will address this topic

²⁵³ Hawkins and Emanuel, “Two Case Studies: Havrix, Surfaxin,” 57.

at length. However, for now, what is important to note is that, as discussed in the introduction, the tested drugs are only be made available at a reasonable rate in developed nations. That was a chief complaint of several Thai scientists in the Havrix trial. There was no provision that ensured that if proven safe and effective the vaccine would be made available to Thailand at a reduced cost. There was, also, an insufficient transfer of technology. Specifically, Thai researchers were not trained to conduct testing for antibody to hepatitis A and other laboratory skills. Most importantly, the scientists argued that Thailand had no interest in the vaccine or expectation of deploy it. As a consequence, the trial did not address a health need of the country, but rather a health interest of the US Army. As the scientists argued, “Thai children who participated were used as ‘testing material’ for the benefit of the U.S. Army and others from developed countries.”²⁵⁴

As discussed in the last chapter, Thomas Pogge points out that one might say that all participants in a trial are benefiting with a placebo control as their chance of receiving effective treatment increases by enrolling in the trial. For example in the Surfaxin case, if half of those enrolled received the Surfaxin treatment and the other half received the placebo, all infants enrolled have had their survival prospects boosted by a 50% chance of receiving the Surfaxin treatment.²⁵⁵ In the last chapter I argue why this argument uses the wrong counterfactual question; however, Pogge provides an additional argument on why this analysis fails. He argues that the harms can be detached from the benefits, but

²⁵⁴ Hawkins and Emanuel, “Two Case Studies: Havrix, Surfaxin,” 58.

²⁵⁵ Pogge, “Testing Our Drugs on the Poor Abroad,” 106.

that those who argue in favor of overall benefit assume that the harms and benefits cannot be detached from each other.

Consider the following analogy:

a rich eccentric is eager to play a paint-bomb prank but wants to make sure it is morally justifiable. So she prepares two gift packages. One contains a paint bomb rigged to open with a loud bang and to splatter the recipient's clothes. The other contains \$30,000. She fills in labels with the names of two persons and assigns the labels to the packages by the flip of a coin. This satisfies our eccentric that she is not harming either recipient. In fact, she is benefitting both by giving each a huge beneficial fifty-fifty chance of \$30,000 or splattered clothing.²⁵⁶

One can see the similarities between this analogy and the Surfaxin case. The trial participants are randomly assigned just as the package recipients are. Each has a fifty-fifty chance of receiving a benefit (the Surfaxin treatment or \$30,000) or a non-benefit (placebo or paint bomb, assuming that the paint bomb is not particularly harmful).

Pogge argues that there are cases where harms cannot be detached from the benefits. In a mandatory vaccination program, we can neither identify which recipients will have an adverse reaction nor alter the vaccine so that it has the same benefit and no one has an adverse reaction. In that case, Pogge maintains “[w]e can then defend the risk of harm to which we expose each child as an undetachable side effect of a program that brings each child an expected net benefit. We can justify this risk to each child.”²⁵⁷ That justification does not work in the paint bomb scenario. The eccentric's claim that “she is probabilistically benefitting both package recipients appeals to an uncertainty that is

²⁵⁶ Pogge, “Testing Our Drugs on the Poor Abroad,” 106-107.

²⁵⁷ Pogge, “Testing Our Drugs on the Poor Abroad,” 107.

entirely of her own making and easily avoidable.”²⁵⁸ The eccentric could detach the harms from the benefit and give money to both individuals.

Similarly, Pogge maintains that the uncertainty of which infants will receive the Surfaxin treatment and which will receive the placebo is entirely of D-Lab’s own making, and is, thus, easily avoidable. The harm is detachable from the benefit because D-Lab could give Surfaxin to everyone or use an ACT. Pogge admits that using an ACT might make the trial more expensive by dispensing more medication and enrolling more subjects, the moral complaint of those infants receiving the placebo is not invalidated. Pogge argues, “it merely shows how this complaint can perhaps be answered by reference to some other good. While the mandatory vaccination program can be justified as treating each child as best we know how, the Surfaxin trial cannot be so justified to the infants in the placebo control group.”²⁵⁹

When evaluating the risk-to-benefit ratio, developing nation participants are taking on more risk than benefits when entering a trial. That is, they are taking on the risks of potential side effects from the experimental drug, potentially being placed in the placebo control, and have their health put at risk by researchers who cut corners. While there is some benefit in infrastructure and in health for those who do receive the experimental drug, the large benefit of improving society’s health through the availability of a new drug at a reasonable price is only garnered by the developed world, not the host nation. More importantly, the developed nations are receiving the benefit of a new drug without taking on any of the risk.

²⁵⁸ Pogge, “Testing Our Drugs on the Poor Abroad,” 107.

²⁵⁹ Pogge, “Testing Our Drugs on the Poor Abroad,” 107.

This tip in balance violates the guidelines used for international research. Recall that both the Declaration of Helsinki and the FDA calls for the benefits to outweigh the risks. CIOMS has two principles that the negative risk-to-benefit ratio violates. These trials violate beneficence, which calls for benefits to be maximized and harms to be minimized, and they violate justice, which calls for the distribution of risks and benefits to be equitable. Even if you do fully accept my risk and benefit analysis for developing nation participants, it is easy to see how the developed world benefits - having access to a new drug - without undertaking any of the risk. This inequitable distribution alone violates CIOMS. However, if you do adopt my counterfactual analysis under which to view risk and benefit, one can see that more risk is being undertaken by developing nations than benefit when we compare the trials to those run in developed nations. This is an additional violation of CIOMS.

Thus, supporters of the standard of care argument are wrong in their assumption that the only relevant research question responsive to the health needs of the host countries is “Is the experimental product being studied better than the ‘nothing’ now available to the population?” First, international guidelines argue that we must evaluate the risk-to-benefit ratio. In doing so, we can see how problematic developing nation trials are. Furthermore, even if we do accept that the only relevant research question is “Is the experimental product being studied better than the ‘nothing’ now available to the population?”, the answer to that question is no. With my risk analysis, we can see that the product being studied is not necessarily better than the nothing now available to the population.

Assumption 3: the only way (or best way) of obtaining affordable products is to test cheap alternatives to replace the expensive ones used in developed nations.

To understand researchers' obligation to provide research garnered from the trial and the experimental drug should it prove effective, let us begin by examining international guidelines. The Declaration of Helsinki makes mention of participants' benefits from research results in two separate sections. In paragraph 17, the Declaration states

[m]edical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that is population or community stands to benefit from the results of the research²⁶⁰

The lynchpin phrase in that paragraph is "reasonable likelihood." It does not say that the researchers must *guarantee* that the community benefits from the results of research, but merely that there is a reasonable chance that the community may benefit. Not only is "reasonable likelihood" a vague phrase that many philosophers and medical experts argue over the meaning, but it allows for a community to not benefit from the results, even if that chance is low, and for a trial to be justifiable. The Declaration goes on to state that participants are entitled to resulting benefits in paragraph 33,

[a]t the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.²⁶¹

Just as in paragraph 17, paragraph 33 does not make any guarantees that the host community will benefit. Rather, it maintains that participants are entitled to that

²⁶⁰ Declaration of Helsinki, paragraph 17

²⁶¹ Declaration of Helsinki, paragraph 33.

information; specifically, they are entitled to *access* to interventions. Access does not mean that pharmaceutical companies must guarantee their receipt of such benefits. It also does not mean that pharmaceutical companies must make that access easy or affordable.

Guideline 10 of CIOM's guidelines directly addresses human research in populations and communities with limited resources;

[b]efore undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:

- the research is responsive to the health needs and priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.²⁶²

Similar to the Declaration of Helsinki, CIOMs relies on a vague phrase, "reasonable availability." What does it mean to make a drug reasonably available to a population? Is allowing the country to buy it, whether they can afford it or not, making the drug reasonably available? While the comments on Guideline 10 go on to describe some of the relevant factors that figure into the calculus, they continue to remain vague on the meaning of "reasonable availability."

As discussed in the introduction, there is a great disparity between the location of the highest prevalence of disease, developing nations, and the location of where the most apt drugs are available, developed nations. With few medical resources and growing epidemics, developed nations are desperate to have access to existing proven medical treatments. As South African bioethicist Solomon Benatar notes,

[t]here are many millions of people around the world who don't have access to the scientific advances of the last hundred years. In fact, if you go to any developing

²⁶² "International Ethical Guidelines for Biomedical Research Involving Human Subjects."

country and ask the people there, they'd say 'Well, we're not so much interested in doing research. We're interested in having access to the things that you have already found that work! Why come here to ask research questions when actually what we need is what has already been discovered! Why should we believe this new research is going to benefit us if the old research doesn't benefit us?'

²⁶³

In response to developing nations' pleas, pharmaceutical companies have launched trials to see if existing medications are effective at lower doses, as a lower dose would be cheaper. This was a motivating factor in the 1997 AZT trial that tested AZT at lower doses, which was responding to the surging AIDS epidemic.

Are lower doses the right solution, or are pharmaceutical companies able to sell existing treatments at a lower rate? In her book The Truth About the Drug Companies, Marcia Angell closely examines the drug industry, looking particularly at the price of drugs and the research and development of new drugs. Pharmaceutical companies argue that drug prices are priced high in order to cover the research and development costs. In 2001, pharmaceutical companies claimed that they spent \$802 million for each new drug that they bring to the market.²⁶⁴

Angell makes many arguments challenging those claims, including the accuracy of the \$802 million figure. I want to focus on her arguments against the tie between research and development costs and drug prices. She argues that there is no reason to believe that research and development costs have anything to do with drug pricing. In reference to the \$802 million figure, the president and CEO of Merck stated, "[t]he price of medicines isn't determined by their research costs. Instead it is determined by their

²⁶³ Solomon Benator quoted in Sonia Shah, *The Body Hunters: Testing New Drugs on the World's Poorest Patients* (New York: The New Press, 2006), 166.

²⁶⁴ Marcia Angell, *The truth about the drug companies: How they deceive us and what to do about it* (New York: Random House Trade Paperbacks, 2005). 37.

value in preventing and treating disease. Whether Merck spends \$500 million or \$1 billion developing a medicine, it is the doctor, the patient, and those paying for our medicines who determine its true value.”²⁶⁵ As Angell points out, what is important about that remark is Mr. Gilmartin’s admission that the price of drugs would remain the same even if research and development costs were to change.

Moreover, pharmaceutical companies are not producing as much original research through their clinical trials as one may think. For example, Burroughs Wellcome, the company that patented AZT, did not develop the technology or provide the first application of that technology that was used to determine if AZT would successfully suppress the HIV virus in human cells. They were also not the first group to run a clinical trial with AIDs patients. All of that was completed by the National Cancer Institute working with staff at Duke University.²⁶⁶ That story is not uncommon. According to Angell at least a third of the big pharma’s drugs are licensed or acquired from an outside source.²⁶⁷

If developing nations are unable to afford brand name drugs, what about generics? To understand the lack of availability of generics, we must examine drug patent law. A patent on a drug lasts twenty years after filing with the U.S. Patent and Trademark Office.²⁶⁸ Once the patent expires, other companies may create generics of the drug.

²⁶⁵ Raymond V. Gilmartin quoted in Marcia Angell, *The truth about the drug companies: How they deceive us and what to do about it* (New York: Random House Trade Paperbacks, 2005). 51.

²⁶⁶ Angell, *The truth about the drug companies*, 26-27.

²⁶⁷ Angell, *The truth about the drug companies*, 57.

²⁶⁸ “Frequently Asked Questions on Patents and Exclusivity,” U.S. Food and Drug Administration, updated December 5, 2012, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm#>.

When generics enter the market, the price of a generic medication can fall as low as twenty percent of the brand-name drug with brand name companies almost never lowering their prices. That combined with the pharmacist's ability to substitute a brand name with a generic unless the doctor specifies otherwise cause brand-name sales to plummet.²⁶⁹

The loss of profit is a great motivator to extend the patents any way possible. Roger L. Williams, former FDA director of pharmaceutical science, observed that there are between ten and twenty different tactics used by pharmaceutical companies to protect their products.²⁷⁰ One of the major aides in their fight is the Drug Price Competition and Patent Term Restoration Act. It was intended to enhance the generic medications market by simplifying the FDA approval process for generic companies. They did not have to test their products in clinical trials; rather, they had to prove that their drug had the same active ingredients as the brand name and that it would act the same way in the body.

While it accomplished its intended job, increasing generic prescriptions from twenty percent in 1984 to fifty percent in 2004, it also created loopholes which pharmaceutical companies have since taken advantage of. The Act had several provisions, which extended patent life. A patent could be extended up to five years if clinical testing and FDA approval created long delays in the drug appearing on the market. Additionally, if a brand-name company sues a generic company for patent infringement, FDA approval of the generic drug will automatically be delayed for thirty months, no matter what the

²⁶⁹ Angell, *The truth about the drug companies*, 174

²⁷⁰ Roger L Williams quoted in Marcia Angell, *The truth about the drug companies: How they deceive us and what to do about it* (New York: Random House Trade Paperbacks, 2005). 174.

merits of the suit are²⁷¹. As Angell explains, these provisions have led to increased efforts to extend their monopoly on a drug,

brand-name drug companies routinely file not just one patent on their blockbusters but a series of them spread throughout the life of the first one. These patents are on every conceivable feature of the drug - never mind usefulness, novelty, or non-obviousness, or how remote from the originally approved drug and its approved use. And remember patents are easy to get. The result is the generic companies are routinely charged with infringement of one of these secondary patents, which immediately triggers thirty months of additional exclusivity.²⁷²

Thirty extra months of exclusivity translates into thirty more months, in addition to the already twenty years, that developing nations have to wait for generics to become available.

In desperate need of HIV medications at an affordable rate, in 1997 the South African legislature amended its Medicines Acts to allow the health minister to break patents and buy cheaper generics during health emergencies or when patented medicines were unaffordable. In response to the amendment, thirty-nine major drug companies went to court to prevent the amendment from being implemented. The trade group Pharmaceutical Research and Manufacturers of America (PhRMA) argued that the law was arbitrary and gave the health minister too many powers. Once again, Angell argues, western interests blocked Africans from accessing lifesaving medicines.²⁷³

If developing nations cannot afford brand-name drugs and the brand-name pharmaceutical companies attempt to prevent generics from being manufactured and sold in developing nations, then pharmaceutical companies have not met their burden of

²⁷¹ Angell, *The truth about the drug companies*, 178-180.

²⁷² Angell, *The truth about the drug companies*, 180-181.

²⁷³ Angell, *The truth about the drug companies*, 102.

providing the research, technology, and experimental drug to the tested community. This tips the risk-to-benefit ratio in favor of developed nations - they receive the benefit without being burdened with the risk.

In order to fulfill that burden, as mentioned, pharmaceutical companies have turned to developing the drug at a lower dose, thus making it more affordable. Not only does that take time, leaving countries without medication for even longer periods of time, but also there is no guarantee that the drug will be effective at the lower dose. Their efforts may be for not. It seems more reasonable and more ethically responsible for brand-name companies to sell their drug at a more affordable rate at the very least for the host country.

Conclusion

In this chapter, I have argued against using the standard of care in the host country as tool by which we design clinical trials. Rather, as I argue throughout, trial participants ought to be treated the same in both developed and developing nations, specifically on the issues of PCTs and the availability of research and the experimented drug after the trial.

There is one objection that I want to address. Some argue that the standard of care gauge is justified because trial participants consent to the terms of the trial. As discussed in the introduction there are major problems with consent in developing countries, but for the purposes of this objection as I have throughout, I will grant all conditions of informed consent are met.

Pogge provides the most compelling argument for why, even under perfect informed consent, the clinical trials designed by the standards of care of the host countries would not be justified or permissible. Consider the following scenario: a successful U.S. filmmaker uses radio equipment waiting for distress calls. She finally hears one; a fishing vessel far out at sea has sprung a leak and is sinking in calm waters. The crew of three from Bangladesh has no flotation devices and will try to survive by treading water. As Bangladesh is a very poor nation, they will not make any efforts to save the crew. Very rarely do ships pass through that part of the sea, and even if another ship heard the call, the ship would be unlikely to make the large detour. The filmmaker radio backs a proposal. She will helicopter to the scene and flip a coin. If it comes up heads, she will rescue the crew and fly them to safety at no charge. If it is tails, she will film whatever happens to them “naturally”, which is most certainly their slow deaths, and promises to save the next crew of fishermen that is in mortal danger. The filmmaker intends to use the footage to make a documentary, which will be filmed in wealthier countries so that audiences may be educated on panic behavior and its effect on human survival in the sea. The crew accepts her offer. It is rational to do so as a fifty percent chance at being saved is far better than guaranteed death. Thus, the filmmaker flips the coin. It comes up tails, and she films their deaths.

Pogge argues, “[t]he case of the filmmaker shows vividly that a recipient’s prior fully informed and rational consent may not justify the treatment he receives as permissible when such consent is exacted as a condition for giving him some chance of

being saved from a horrible predicament.”²⁷⁴ In other words, consent does not justify the filmmaker’s actions as the crew was placed in a situation where they had no bargaining power to change the conditions of the agreement. Under those circumstances, the filmmaker could have taken even worse actions - making the fishermen promise to give her all savings - and so long as her conditions were better than death, the fishermen are rational to agree.

The filmmaker case is analogous to the clinical trials situation. Trial participants are suffering from diseases and infections with no hope of treatment. Most would be willing to make great sacrifices for a chance at getting treatment. Their consent does not, however, justify using placebos or withholding the experimental treatment after the trial is completed when pharmaceutical companies have the means to save them.

²⁷⁴ Pogge, “Testing Our Drugs on the Poor Abroad,” 109-100.

Chapter 5: Conclusion

I have argued that the double standard in clinical research between those run in developing nations versus developed nations is exploitative to the developing nation participants and host countries. Trials run in developing nations continue to increase. Pharmaceutical companies and other research bodies are attracted to developing nations for many reasons including: financial benefit, high numbers of volunteers, and low dropout rates. By looking at cases such as AZT and Surfaxin, we saw the many double standards between trials run in developing nations versus developed nations. Particularly, researchers are using a placebo control when a known effective treatment exists and is available to the general public in developed nations. This violates clinical equipoise which demands that a trial end when it is known which treatment - the control or experimental - is more effective. Additionally, pharmaceutical companies and researchers are not providing the experimental treatment to the host developing nation if the treatment is proven effective. This is unfair to developing nations given that the risks and benefits of a trial are to be balanced for participants. Since drug prices are too high for developing nations to afford, they do not have access to the benefits of the trial. Thus, developing nations are taking all the risk but are not being afforded the benefits.

The best lens under which to view the wrongdoing of the double standards in clinical research is exploitation. In its most minimal sense, exploitation means to take advantage of something or someone. Intuitively it seems that pharmaceutical companies are taking advantage of developing nations and their lack of access to healthcare. Exploitation, also, provides a lens that is able to unify many research concerns. Finally, the language surrounding the clinical research double standards centers heavily on

exploitation. Therefore, it seems only appropriate to use the language and model already accepted in the literature.

Once we accept exploitation as the appropriate lens, we can see the difficulty existing theories have in explaining why the double standard is exploitative. This difficulty arises from viewing clinical research in developing nations as mutually beneficial. That is, both the researchers and trial participants benefit. Trial participants benefit as they are left better off than they would have been had the trial not taking place. That is, they receive medical care in the trial versus the no treatment if the trial does not take place. I look at three different approaches to exploitation. Alan Wertheimer argues that exploitation is when A gains from a transaction or action that is harmful to B, where harm is defined in terms of an appropriate baseline. Mutually beneficial exploitation is when A unfairly gains or gains in an excessive amount from a transaction that is beneficial to B. Though he initially defines the baseline in terms of the competitive market value, he later rejects that in favor of an appropriate normative standard to be chosen. The problem with Wertheimer's account is that he offers no mechanism for determining what the normative standard ought to be, especially in the case of clinical research.

John Lawrence Hill argues that an interaction is exploitative if it

- 1) consist of an offer of benefit, never a threat
- 2) which is made intentionally, knowingly or recklessly on the part of the offeror, such that it is likely to involve, implicate or take advantage of;
- 3) a psychologically recognized vulnerability or weakness on part of the offeree;
- 4) where the vulnerability or weakness characteristically results in a significant impairment of the rational-emotional capacity of the individual;
- 5) that the offer actually has the effect of impairing the rational-emotional capacity of the offeree;

- 6) such that, but for the impairment of this capacity, the offeree would not have accepted the offer.²⁷⁵

Hill's account is problematic for many reasons, the primary of which is that it stipulates that it is not rational for the victim to enter into an exploitative transaction. However, in the case of clinical research it seems perfectly rational for the developing nation citizen to enter the trial. He has a chance of receiving lifesaving treatment by entering versus the zero treatment he receives if he does not.

Finally, Ruth Sample maintains that exploitation "involves interacting with another being for the sake of advantage in a way that degrades or fails to respect the inherent value in that being."²⁷⁶ Sample's theory is very broad and relies on the phrase "to take advantage." Such broadness leads to many cases of wrongdoing that do not seem exploitative to be categorized as exploitation, such as murder.

Because I am dissatisfied that any single theory can account for all cases of exploitation, I proposed defining the necessary and sufficient for a type of exploitation rather than for exploitation as a whole. I call the type of exploitation I am interested in comparative exploitation. In comparative exploitation, A exploits B in interaction I iff

1. A does x to B in interaction I; and
2. there is a possible world in which C exists such that (1) B and C ought to be treated equally; (2) if A and C engage in I under similar circumstances, A does not do x to C; (3) it is feasible for A to not do x to B; and
3. A treats B less equally than A has treated, treats, or would treat C in interaction I for the sake of benefit.

²⁷⁵ Hill, "Exploitation," 683-4

²⁷⁶ Sample, *Exploitation*, 57.

The problem of clinical research is one of comparative exploitation. The A is the researchers, the B is developing nation participants, and the C is developed nation participants. Researchers are exploiting developing nation participants because developing nation participants and developed nation participants ought to be treated equally; it is possible for researchers to treat both groups equally; and researchers are treating developing nation participants less equally than developed nation participants.

Under my vision of comparative exploitation, clinical research exploitation, like many other cases of mutually beneficial exploitation, is erroneously considered mutually beneficial. Under the traditional counterfactual account of harm, to suffer a harm is to come to be worse off than one otherwise would have been. In an effort to be charitable to counterfactual account defenders, Matthew Hanser provides the following formulation of the counterfactual comparison of harm: “a person suffers harm if and only if there occurs an event *e* such that had *e* not occurred he would have been better off in some respect *for some interval of time*.”²⁷⁷ Two of the problems Hanser identifies with this account are preemptive harms and excessive multiplication of harm.

Ben Bradley offers a different account of harm that is not only able to solve the problems of preemptive harms and excessive multiplication of harm, but also explains why exploitation in clinical research, along with many other exploitation cases erroneously labeled as mutually beneficial, is harmful. For Bradley, in order to understand the value of an action, we should focus on the following counterfactual conditional: “if X were to have happened, Y would have happened.”²⁷⁸ He understands

²⁷⁷ Sample, *Exploitation*, 424.

²⁷⁸ Bradley, *Well-being and Death*, 48.

that statement to mean “to say that if X were to have happened, Y would have happened is to say that at the closest possible world in which X happens, Y happens.”²⁷⁹ In determining which possible world is closest to the actual world, one must adopt a similarity relation. Because different similarity relations change which possible world is closest to the actual world, the value of an action must be relativized to that particular similarity relation.

I accept Bradley’s account of harm and argue that for comparative exploitation, specifically clinical research exploitation, we ought to ask a counterfactual question using a similarity relation in which in the closest possible world is one in which the interaction is nonexploitative. Because developing nation participants would receive benefits in that possible world that they do not receive in the actual world, developing nation participants are being harmed.

If we do not accept Bradley’s account of harm, I argue that comparative exploitation is still an all-things-considered harm and would be deemed harmful under the traditional counterfactual account. When A comparatively exploits B, A is promoting an exploitative attitude, one that publicizes B’s vulnerability to exploitation. That attitude creates a climate of harm under which B, and individuals like B, are more likely to get exploited, which increases the likelihood that B will get harmed. Furthermore, even if A does not harm B in their exploitative transaction, the likelihood of severe harm increases. Thus, under a traditional counterfactual comparison, it is better for A and B to not interact than for A to comparatively exploit B.

²⁷⁹ Bradley, *Well-being and Death*, 48.

One challenge to claims of exploitation in clinical research is that participants in developing nations and developed nations should not be treated similarly. Rather, the restraints for the trial, specifically the control group, ought to be determined by whatever the “standard of care” is for the host country. Thus, if the known effective treatment is not available in the host country, it is acceptable to use a placebo control. I argue that while international guidelines are vague, they do not necessarily support the standard of care argument. Furthermore, those who support the different treatment are making three faulty assumptions, as identified by Ruth Macklin: placebo-controlled trials are the gold standard even in circumstances where using that methodology compromises ethical standards; the only relevant research question responsive to the health needs of the host countries is “Is the experimental product being studied better than the ‘nothing’ now available to the population?”; and the only way (or best way) of obtaining affordable products is to test cheap alternatives to replace the expensive ones used in developed nations. In response, I argue that active-controlled trials provide a reliable alternative to the placebo control. I also contend that the experimental drug is not better than the ‘nothing,’ but that another relevant research question concerns the risk-to-benefit ratio for trial participants as mandated by international and FDA guidelines. Finally, I maintain that pharmaceutical companies are not fulfilling their burden of making the drug available to the tested population, and that it is conceivable for those companies to sell the drug at a cheap price.

In sum, researchers are comparatively exploiting developing nation participants by offering them less than they would had the participants lived in a developed nation. That exploitation is not only morally wrong, but it is harmful to the participants and the

host nation. In order to avoid that exploitation, we must move towards universalizing the standards for clinical trials.

One More Problem

If we accept my account to be true, clinical research is exploitative and we ought to universalize conditions for trials in developed and developing countries, there still exists one major worry: there will no longer be an incentive for trials to be run in developing nations. Thomas Pogge elaborates on this worry using Discovery Lab's (D-Lab) Surfaxin trial. He argues that D-Lab has no good reason to run the trial in Bolivia unless it can use a placebo control. Thus, D-Lab has three feasible options for testing Surfaxin.²⁸⁰ They are ranked as follows in nonmoral, cost-benefit terms:

Placebo-Poor: use a placebo-control design and conduct the test in a poor country;

Active-Rich: use an active-control design and conduct the test in a rich country;

Active-Poor: use an active-control design and conduct the test in a poor country.²⁸¹

As described in Chapter 4, placebo controls are economically advantageous for pharmaceutical companies, hence why the *Placebo-Poor* option ranks first. Moreover, it is cheaper for a company to run an active control design in a rich country, as they would not have to provide the additional infrastructure and supplies that is often required in developing nations. Recall the Havrix trial where researchers provided medical supplies, training, and wireless networking to the community in Thailand. Those items need not be provided by the sponsoring research company in developed nations, as they are already

²⁸⁰ He rules out the option of running a placebo control in a developed nation as it is universally accepted as immoral and illegal.

²⁸¹ Pogge, "Testing Our Drugs on the Poor Abroad," 116.

apart of existing infrastructure. Thus, the *Active-Rich* option is more financially attractive than the *Active-Poor* option.

Pogge notes that “[w]hen morality places constraints on what an agent may demand from needy people in exchange for improving their situation, may such agents tend to ignore the plight of the needy people.”²⁸² Therefore, as Pogge suggests, even though developing nations are in desperate need of medical attention that clinical trials can afford, we can reasonably expect fewer trials to be run in developing nations if standards are universalized. The benefit at stake for developing nations is huge. Even though the host nation and trial participants, particularly those in the placebo control, are being exploited, those receiving the experimental drug are receiving beneficial medical treatment that may prevent death. In the Surfaxin example, if the trial is not run in Bolivia, then those infants in the experimental group are not receiving the Surfaxin and will surely die of respiratory distress syndrome. And, that is exactly what happened. After receiving international criticism, D-Lab ran an active control trial in the United States.²⁸³

Agreeing with Pogge’s assessment, Alan Wertheimer suggests that to interfere with the exploitative interaction between developed nation researchers and developing nation trial participants may be better for no one. He is not arguing that it is morally permissible for researchers to exploit trial participants, but rather that it is wrong to prevent such a transaction, where both parties benefit in some way, on the grounds that such transactions are unfair. Wertheimer calls that argument the Permitted Exploitation

²⁸² Pogge, “Testing Our Drugs on the Poor Abroad,” 122.

²⁸³ Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 244.

Principle (PEP).²⁸⁴ There are arguments for rejecting PEP, Wertheimer admits, including appeals to justice or ethical obligations. However, there are plausible justifications for PEP, including the welfare of the exploited party. Wertheimer believes that the question of whether to permit the exploitative interaction in clinical drug trials is an empirical question of effects. If developing nation participants are going to be significantly worse off without the trial, then there seems to be a justification for permitting the interaction.²⁸⁵

I disagree with Pogge and Wertheimer's assessment. While there is a possibility of clinical trials declining in developing nation with the universalization of standards, there are additional reasons beyond the cost effectiveness of placebo controls for researchers to run trials in developing nations. These were identified in Chapter 1 and include: cheaper labor costs, rapid recruitment of participants, low dropout rates and participant complaints, and lower risk of drug interactions. While D-labs may have altered their plan in the face of criticism, it is unclear whether it will be empirically true of all researchers and pharmaceutical companies given those listed advantages.

Moreover, the deeper concern is whether to permit such exploitation in light of the potential decline of trials in developing nations. I, firmly, disagree with PEP within this context. First, as I argued in Chapter 3, it is a misconception to believe that trial participants are not being harmed through the exploitative transaction. Since there are benefits that developing nation participants are not receiving that developed nation participants are, developing nation participants are being harmed when we conceive of harm under Bradley's lens. Additionally, as Larry Mays argues, when researchers exploit

²⁸⁴ Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 219.

²⁸⁵ Wertheimer, *Rethinking the Ethics of Clinical Research: Widening the Lens*, 243-244.

trial participants, even if those trial participants are not harmed, the researchers are creating a climate of harm that increases the likelihood of harm to developing nations. Thus, while in the short term it may be agreeable to allow exploitative drug trial practices to continue, in the long term developing nations may suffer extensive harm. That justifies intervention of exploitative transactions even if there is a low probability of harm from that transaction.

Second, even if we disregard my harm analysis and accept that trial participants are benefited from the exploitative transaction, a moral wrong is still being done when the participants are exploited. As a society, it seems we ought to intervene out of a deeper sense of justice. Do not the trial participants deserve to be interacted with in a fair nonexploitative manner? If we deem the exploitative transactions to be permissible then society is in a sense being held hostage by the exploiter, the pharmaceutical companies. In essence, the threat is to withdraw potentially lifesaving drug trials from developing nations if we hold them morally accountable for their actions. Not only is this a bad practice for determining what we ought or ought not to do, but also it creates a dangerous slippery slope. If we adopt a policy of allowing morally wrong actions that seemingly benefit the victim, then what prevents society from giving in on other moral wrongs, where the harm to the victim is more evident, when in similar hostage type situations? In other words, where do we draw the bright line on permissibility of morally wrong actions?

Third, there is a need to intervene in exploitative clinical trials because, as Pogge argues, pharmaceutical companies are partly at fault for why quality healthcare is not available in developing nations. Recall that in Chapter 4, I explain how pharmaceutical

companies, through manipulation of patent law and lobbying efforts, keep the price of drugs high. A major consequence of which is that developing nations are unable to afford such medication and go without. Moreover, the persistent impoverished state of many developing nations is also in part a result of the existing global economic order. As Pogge explains, “insofar as the existing global economic order, through its strong centrifugal tendencies, contributes to the persistence of severe poverty in many poor countries, the most powerful states and their corporations and citizens, playing the dominant role in designing and imposing this order, share responsibility for such poverty.”²⁸⁶ As members that both contribute to and benefit from the global economic systems, pharmaceutical companies are excluding most people in poor countries from accessing lifesaving medications before even entering the country to run a trial. As Pogge rightly suggests, while exploitation through clinical trials is morally wrong, that moral wrongness is made worse when the exploitation is able to occur as the result of an injustice the pharmaceutical companies help create.²⁸⁷

Furthermore, though moral constraints may create the permissible exploitation dilemma, morality can provide the solution. As Pogge argues,

[m]orality can hold that people with ample resources (money, time, etc.) ought to make some effort toward preempting and reducing such root causes of severe distress. If most affluent people, corporations, and governments gave a little of their wealth toward reducing severe poverty or toward beefing up emergency services (hospitals, ambulances, coast guard, fire brigade), then we could avoid and preempt most of the desperate needs and emergencies that agents such as D-Lab . . . are tempted to take advantage of.²⁸⁸

²⁸⁶ Pogge, “Testing Our Drugs on the Poor Abroad,” 114.

²⁸⁷ Pogge, “Testing Our Drugs on the Poor Abroad,” 114-115.

²⁸⁸ Pogge, “Testing Our Drugs on the Poor Abroad,” 123.

Such a position is aimed towards achieving basic health care across all nations.²⁸⁹ This would in turn eliminate the injustice that pharmaceutical companies are taking advantage of when they exploit developing through clinical drug trials.

Pogge's solution is an ideal one that reflects a deeper worry over economic disparity between nations. That is not very helpful with our current dilemma over whether to allow exploitative clinical trials in developing nations because if we prohibit them, then trials may not be run in developing nations at all. Accepting the overarching ideal of health care equality to frame the issue, Pogge also suggests practical solutions.

Pogge admits that holding pharmaceutical companies to a moral responsibility to alleviate the medical disaster among the global poor is a large task for a single company. As he describes,

[i]f one of them lived up to its moral responsibility - by making a major research effort targeted at poor-country diseases, for example, or through a massive initiative of offering proprietary drugs cheaply to poor people in developing countries - then it would quickly encounter the discipline of the market. It would face declining revenues with which to fund its research, gradually lose ground against its competitors, and eventually end up in bankruptcy.²⁹⁰

However, an effort made by pharmaceutical companies *together* may be create effective change in developing nation while not overburdening the companies.²⁹¹

Assuming a *public-good* strategy, that is aiming reformatations at what is good for the public, Pogge offers three practical reforms on how we may achieve that change.

First, "the results of any successful effort to develop (research, test, and obtain regulatory approval for) a new essential drug are to be provided as a public good that all

²⁸⁹ Pogge, "Testing Our Drugs on the Poor Abroad," 124.

²⁹⁰ Pogge, "Testing Our Drugs on the Poor Abroad," 125-126.

²⁹¹ Pogge, "Testing Our Drugs on the Poor Abroad," 126.

pharmaceutical companies may use free of charge.”²⁹² This suggestion counteracts the problem of high drug prices brought on by drug patents. That is, if research is available to all, other companies may produce the drug. This, in turn, creates competition, which drives the price of drugs down close to their cost of production.²⁹³

If we were to accept the first reform in isolation, there would be little incentive for pharmaceutical companies to spend money and effort in research. This leads to Pogge’s second reform,

inventor firms should be entitled to take out a multiyear patent on any essential medicines they invent, but during the life of the patent, should be rewarded out of public funds, in proportion to the impact of their invention on the global disease burden.²⁹⁴

This reform restructures the incentive structure for such firms. As Pogge describes,

any inventor firm would have incentives to sell its innovative treatments cheaply. . . in order to help get its drugs to even very poor people who need them. It would have incentives also to ensure that patients are fully instructed in the proper use of its drugs (dosage, compliance, etc.) so that, through wide and effective deployment, they have as great an impact on the global disease burden as possible.²⁹⁵

Pogge also suggests that this would encourage pharmaceutical companies to work with generic producers, as the copying of the drug by generic producer increases the number of patients receiving the drug, which would, in turn, increase the favorable impact on the global disease burden.

²⁹² Pogge, “Testing Our Drugs on the Poor Abroad,” 128.

²⁹³ Pogge has a more complex explanation of how one might conceive of a temporary monopoly scheme or differential-pricing strategy. For my purposes, it is only important to understand the suggestion as free access to research to drive costs down.

²⁹⁴ Pogge, “Testing Our Drugs on the Poor Abroad,” 129.

²⁹⁵ Pogge, “Testing Our Drugs on the Poor Abroad,” 129.

An additional advantage of such a model is that it would encourage companies to research diseases that are predominantly in poorer nations, such as tropical diseases.²⁹⁶ Little research is conducted on such diseases, as there is little profit margin for the pharmaceutical company. However, it is reasonable to think that the financial gain for improving the global disease burden would lead companies to research more tropical diseases. One might think that this would, thus, reduce research on medical conditions that add little to the global disease burden. In anticipation of such a concern, Pogge limits the new incentive scheme to *essential* drugs. Drugs for other medical conditions would remain under the existing incentive model.²⁹⁷

Because the second reform requires a funding source for the incentives, Pogge suggests a third reform, “to develop a fair, feasible, and politically realistic allocation of these costs, as well as compelling arguments in support of this allocation.”²⁹⁸ In order for implementation to be successful the majority of the burden of cost will rest on developed nations’ shoulders. Pogge offers give prudential reasons justifying developed nations’ shouldering the majority of the financial burden. First, taxpayers in developed nations substantially benefit from the lower drug costs and/or insurance premiums. Second, “by giving poor populations a free ride on the pharmaceutical research conducted for citizens in the affluent countries, we are building goodwill in the developing countries by demonstrating in a tangible way our concern for their horrendous public health problems.”²⁹⁹ Third, medical-research jobs in would be created in developed nations.

²⁹⁶ Pogge, “Testing Our Drugs on the Poor Abroad,” 129.

²⁹⁷ Pogge, “Testing Our Drugs on the Poor Abroad,” 130.

²⁹⁸ Pogge, “Testing Our Drugs on the Poor Abroad,” 131.

²⁹⁹ Pogge, “Testing Our Drugs on the Poor Abroad,” 132.

Fourth, the reform would rapidly increase medical knowledge with a broader array of medical interventions, which would enable developed nations to better respond to public health emergencies. Fifth, better human health globally reduces the threat developed nations face from invasive diseases.³⁰⁰

It is not my intention to advocate or defend Pogge's reforms. Even he admits that his proposed reforms need to be better developed and more thought through.³⁰¹ I merely want to show that there are possible solutions to maintaining clinical research in developing nations without sacrificing our moral standards for clinical trials. Thus, rather than continuing to center on morally evaluating the double standards in clinical research, the future debate should focus on crafting reformatory plans that can equalize the playing field between developed and developing nations.

³⁰⁰ Pogge, "Testing Our Drugs on the Poor Abroad," 132.

³⁰¹ Pogge, "Testing Our Drugs on the Poor Abroad," 133.

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